CONTEMPORARY PEDIATRICS OCTOBER 2014 VOL. 31 NO.10

Contemporary PEDIATRICS®

OCTOBER 2014
VOL. 31 | NO. 10

PUZZLER
Lymphadenopathy leads to heart failure

Expert Clinical Advice for Today's Pediatrician

ContemporaryPediatrics.com

CEFACLOR

For Oral Suspension, USP

125 mg/5ml · 250 mg/5ml · 375 mg/5ml

CONTRAINDICATION

- Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

- BEFORE THERAPY WITH CEFACLOR IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFACLOR, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.
- Antibiotics, including Cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.
- Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including Cefaclor, and may range in severity from mild diarrhea to fatal colitis.

PRECAUTIONS

- Prescribing Cefaclor in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increase the risk of the development of drug-resistant bacteria. Prolonged use of Cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.
- Cefaclor should be administered with caution in the presence of markedly impaired renal function.
- As with other b-lactam antibiotics, the renal excretion of Cefaclor is inhibited by probenecid.
- Antibiotics, including cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

ADVERSE EFFECTS

- The most common adverse effects associated with treatment with Cefaclor include hypersensitivity reactions (1.5%) and gastrointestinal symptoms (2.5%), including diarrhea.

For complete safety information, see Full Prescribing Information.

Report suspected adverse reactions to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

[1] Pediatrics.aappublications.org/principles of judicious antibiotic prescribing for URTI in Pediatrics

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DERMATOLOGY ISSUES

MANAGING ECZEMA

+ *Sunscreen Guidelines*
New Acne Findings
Bumps on Baby's Heels

PEER-REVIEWED

Cystic Fibrosis
An essential update

ADVANSTAR
MEDICAL COMMUNICATIONS GROUP

NEW ways to take Vyvanse

Consider Vyvanse for patients who request an alternative to swallowing capsules

To mix[1]:

- Open capsule and mix contents with yogurt, OJ, or water until completely dispersed
- Stir to break apart any compacted powder
- Consume **immediately** (do not store)
- Take full contents of capsule (do not divide)

Vyvanse is indicated for the treatment of ADHD in patients ages 6 and above.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

- **CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence.**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.**

- Contraindications:
  - Known hypersensitivity to amphetamines or other ingredients in Vyvanse. Anaphylactic reactions, Stevens-Johnson syndrome, angioedema, and urticaria have been observed in postmarketing reports.
  - Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of Vyvanse within 14 days of the last MAOI dose. Hypertensive crisis can occur.
- Educate patients about abuse and periodically re-evaluate the need for Vyvanse.
- Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Prior to treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Vyvanse treatment.
- CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychosis. Clinical evaluation for bipolar disorder is recommended prior to stimulant use.

Reference: 1. Vyvanse [package insert]. Wayne, PA: Shire US Inc.

Vyvanse® can be mixed with yogurt, orange juice, or water[1]

Dosing[1]:

- Recommended starting dose: 30 mg once daily in the morning. Avoid afternoon doses due to potential for insomnia
- Increase in increments of 10 mg or 20 mg at approximately weekly intervals if needed
- Maximum dose: 70 mg per day

Flexible administration options:
mix contents with yogurt, orange juice, water, or swallow whole[1]

IMPORTANT SAFETY INFORMATION

- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Monitor weight and height in children during treatment with Vyvanse. Treatment may need to be interrupted in children not growing as expected.
- Stimulants used to treat ADHD, including Vyvanse, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes (e.g., numbness, pain, skin color change, or sensitivity to temperature, and rarely ulcerations and/or soft tissue breakdown) is necessary during treatment and may require further evaluation (e.g., referral).
- The most common adverse reactions (≥5% and at least twice the rate of placebo) reported in clinical trials were:
  - *Children aged 6 to 12:* decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, decreased weight, nausea, dry mouth and dizziness;
  - *Adolescents aged 13 to 17:* decreased appetite, insomnia, and decreased weight;
  - *Adults:* decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety and anorexia.
- Vyvanse is in Pregnancy Category C. Vyvanse should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Amphetamines are excreted into human milk and there is the potential for serious adverse reactions in nursing infants.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNING regarding Potential for Abuse and Dependence, on the following pages.

ONCE-DAILY
Vyvanse® II
(lisdexamfetamine dimesylate)
20 • 30 • 40 • 50 • 60 • 70 mg capsules

Vyvanse® (lisdexamfetamine dimesylate) Capsules
20, 30, 40, 50, 60, 70 mg CII Rx Only

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

INDICATIONS AND USAGE

Vyvanse® is indicated for treatment of Attention Deficit Hyperactivity Disorder (ADHD).

DOSAGE AND ADMINISTRATION

- Recommended starting dose: 30 mg once daily in the morning in patients ages 6 and above
- Increase in increments of 10 or 20 mg at approximately weekly intervals if needed
- Maximum dose: 70 mg per day
- Prior to treatment, assess for presence of cardiac disease

CONTRAINDICATIONS

Vyvanse is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports.
- Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of Vyvanse within 14 days of the last MAOI dose. Hypertensive crisis can occur.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence *(See Boxed Warning Above)*

Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Vyvanse treatment.

Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode.

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing the CNS stimulant. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Vyvanse. In a 4-week, placebo-controlled trial of Vyvanse in patients ages 6 to 12 years old, there was a dose-related decrease in weight in the Vyvanse groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height.

Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including Vyvanse, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect rates observed in practice.

The safety data in this section is based on data from 4-week parallel-group controlled clinical studies of Vyvanse in pediatric and adult patients with ADHD.

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled trial in patients ages 6 to 12 years, 9% (20/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)].

In the controlled trial in patients ages 13 to 17 years, 4% (10/233) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

In the controlled adult trial, 6% (21/358) of Vyvanse-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More Among Vyvanse-Treated Patients in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, adolescent patients ages 13 to 17 years, and adult patients treated with Vyvanse or placebo are presented in Tables 1, 2, and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	Vyvanse (n=218)	Placebo (n=72)
Decreased Appetite	39%	4%
Insomnia	23%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	Vyvanse (n=233)	Placebo (n=77)
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

	Vyvanse (n=358)	Placebo (n=62)
Decreased Appetite	27%	2%
Insomnia	27%	8%
Dry Mouth	26%	3%
Diarrhea	7%	0%
Nausea	7%	0%
Anxiety	6%	0%
Anorexia	5%	0%
Feeling Jittery	4%	0%
Agitation	3%	0%
Blood Pressure Increased	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Weight Decreased	3%	0%
Dyspnea	2%	0%
Heart Rate Increased	2%	0%
Tremor	2%	0%

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on Vyvanse and 0% on placebo; decreased libido was observed in 1.4% of subjects on Vyvanse and 0% on placebo.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Vyvanse. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, tics, bruxism, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, and constipation.

DRUG INTERACTIONS

Acidifying and Alkalinizing Agents

Ascorbic acid and other agents that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine. Adjust the dosage accordingly.

Monoamine Oxidase Inhibitors

Do not administer Vyvanse concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

Effect of Other Drugs on Vyvanse:

From a pharmacokinetic perspective, no dose adjustment of Vyvanse is necessary when Vyvanse is coadministered with guanfacine, venlafaxine, or omeprazole.

Effect of Vyvanse on Other Drugs

From a pharmacokinetic perspective, no dose adjustment of CYP1A2, CYP2D6, CYP2C19, and CYP3A4 substrates (caffeine, dextromethorphan, omeprazole, and midazolam, respectively) are necessary when Vyvanse is coadministered. In addition, no dose adjustment of guanfacine or venlafaxine is needed when Vyvanse is coadministered.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.: Risk Summary

There are no adequate and well-controlled studies with Vyvanse in pregnant women. Vyvanse should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Amphetamines are excreted into human milk. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Geriatric Use

Clinical studies of Vyvanse did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Special Populations

Figure 3: Special Populations:

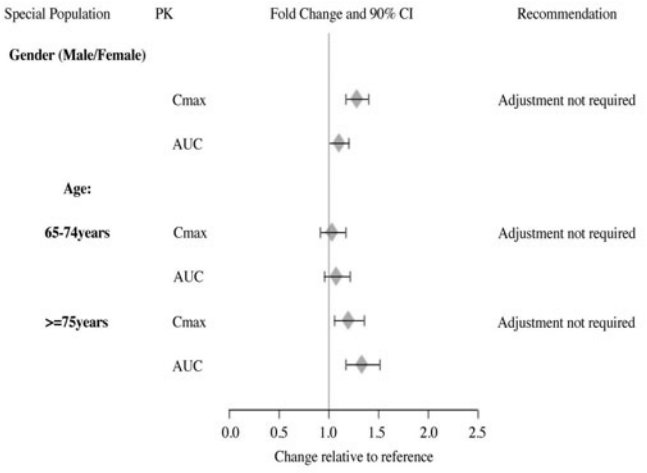

*Figure 3 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference.

DRUG ABUSE AND DEPENDENCE

Vyvanse contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Manufactured for: Shire US Inc., Wayne, PA 19087
Made in USA
For more information call 1-800-828-2088

US Pat No. 7,105,486 and US Pat No. 7,223,735
Last Modified: 7/2014
S03276

Shire

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content

TERESA MCNULTY
Content Channel Director
440.891.2728 / tmcnulty@advanstar.com

CATHERINE M RADWAN
Content Managing Editor
440.891.2636 / cradwan@advanstar.com

MIRANDA HESTER
Content Specialist

KATHRYN FOXHALL
MARIAN FREEDMAN
Contributing Editors

ROBERT MCGARR
Group Art Director

NICOLE DAVIS-SLOCUM
Art Director

KAREN LENZEN
Senior Production Manager

publishing & sales

GEORGIANN DECENZO
Executive Vice President
440.891.2778 / gdecenzo@advanstar.com

KEN SYLVIA
Vice President, Group Publisher
732.346.3017 / ksylvia@advanstar.com

DIANE CARPENTERI
National Account Manager
732.346.3092 / dcarpenteri@advanstar.com

MARGIE JAXEL
Dir. of Business Develpment, Healthcare Technology Sales
732.346.3003 / mjaxel@advanstar.com

PATRICK CARMODY
Account Manager, Healthcare Technology
440.891.2621 / pcarmody@advanstar.com

JOAN MALEY
Account Manager, Classified/Display Advertising
440.891.2722 / jmaley@advanstar.com

JOANNA SHIPPOLI
Account Executive, Recruitment Advertising
440.891.2615 / jshippoli@advanstar.com

DON BERMAN
Business Director, eMedia
212.951.6745 / dberman@advanstar.com

MEG BENSON
Special Projects Director
732.346.3039 / mbenson@advanstar.com

GAIL KAYE
Director of Marketing & Research Services
732.346.3042 / gkaye@advanstar.com

HANNAH CURIS
Sales Support
732.346.3055 / hcuris@advanstar.com

RENEE SCHUSTER
List Account Executive
440.891.2613 / rschuster@advanstar.com

MAUREEN CANNON
Permissions
440.891.2742 / mcannon@advanstar.com

audience development

JOY PUZZO
Corporate Director
440.319.9570 / jpuzzo@advanstar.com

CHRISTINE SHAPPELL
Director
201.391.2359 / cshappell@advanstar.com

WENDY BONG
Manager
218.740.7244 / wbong@advanstar.com

REPRINTS
877.652.5295 ext. 121 / bkolb@wrightsmedia.com
Outside US, UK, direct dial: 281.419.5725. ext. 121

CUSTOMER SERVICE
888.527.7008

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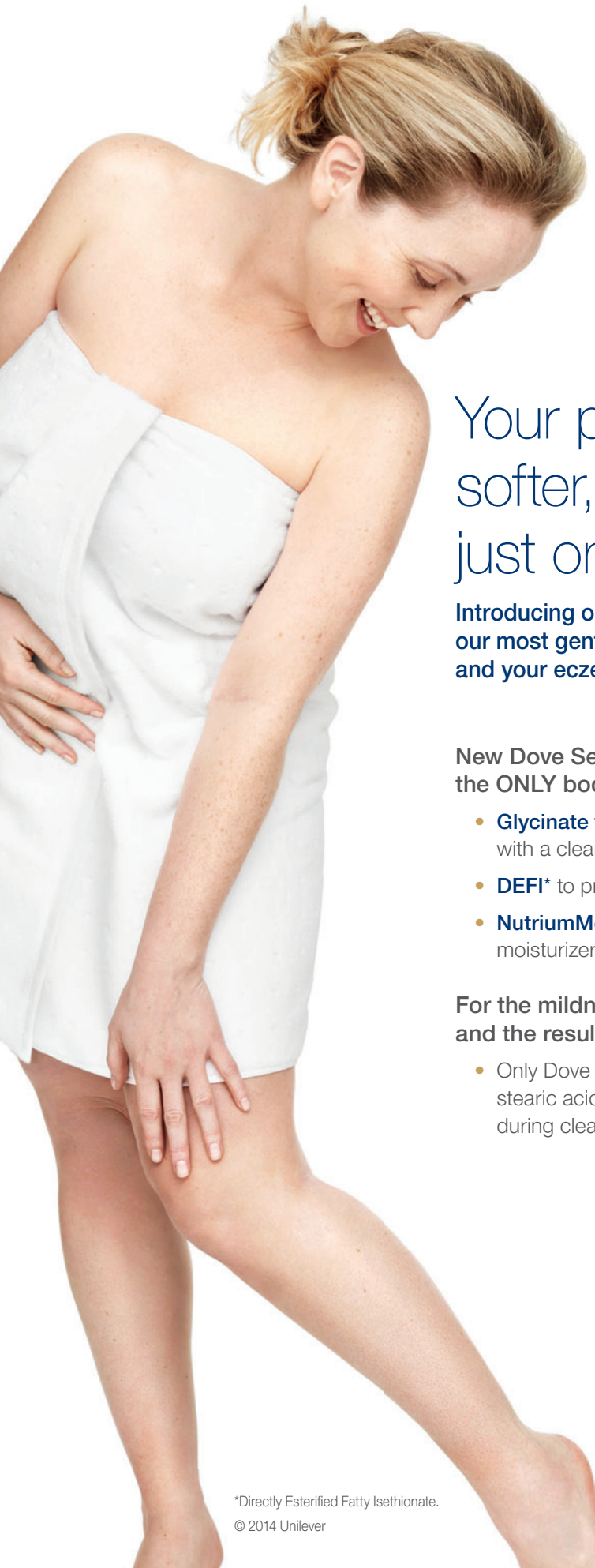

Your patients will feel softer, smoother skin after just one shower

Introducing our mildest formula ever, using only our most gentle surfactants—mild enough for infants and your eczema patients

New Dove Sensitive Skin Body Wash is the ONLY body wash that includes:

- **Glycinate** for its mildness and excellent lathering ability with a clean rinse
- **DEFI*** to preserve and replenish skin lipids, and
- **NutriumMoisture®**, a unique blend of 100% skin-natural moisturizers that can be fully absorbed in the skin

For the mildness and moisturization you want and the results your patients will love

- Only Dove is proven to replenish stearic acid, a fatty acid that is easily removed during cleansing, at a 1-to-1 ratio

*Directly Esterified Fatty Isethionate.

Contemporary PEDIATRICS®

October 2014
VOL. 31 NO. 10

special report: dermatology

peer-reviewed article

20 puzzler

44 peds v2.0

50 dermcase

departments

in addition

Contemporary Pediatrics (Print ISSN: 8750-0507, Digital ISSN: 2150-6345) is published monthly by Advanstar Communications, Inc., 131 W. 1st Street, Duluth, MN 55802. Subscription rates: one year $89, two years $150 in the United States & Possessions, $105 for one year, $189 for two years in Canada and Mexico; all other countries $105 for one year, $189 for two years. Single copies (prepaid only) $18 in the United States; $22 in Canada and Mexico, and $24 in all other countries. Include $6.50 per order plus $2.00 per additional copy for U.S. postage and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to Contemporary Pediatrics, PO Box 6083, Duluth, MN 55806-6083. Canadian GST number: R-124213133RT001. Publications Mail Agreement Number 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA . Printed in the U.S.A.

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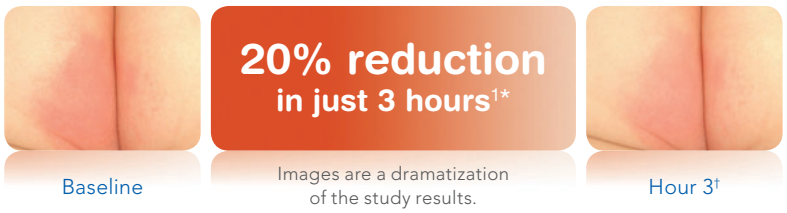
Fast relief. Proven results.

STRONG CLINICAL DATA STRENGTHENS YOUR RECOMMENDATION

DESITIN® Maximum Strength Original Paste

Fast reduction in erythema

- Statistically significant reduction of erythema in just 1 diaper change[1]



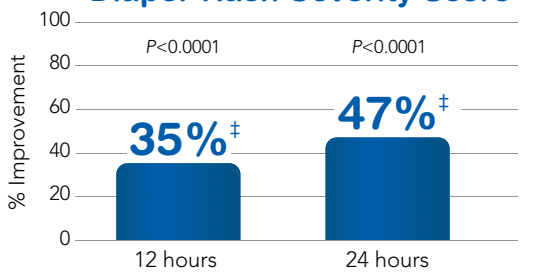
*Trial assessing the efficacy of DESITIN® Maximum Strength Original Paste for 3±1 hours in children (N=31) 3-36 months of age, with mild to moderate diaper rash, wearing diapers for 24 hours a day.[1]

†*P*=0.0001

Effective improvement in skin health

- Evaluation of erythema, papules, and dryness/scaling
- An average improvement score of **35% at 12 hours** (*P*<0.0001) and **47% at 24 hours** (*P*<0.0001)[2‡]

Significant Improvement in Diaper Rash Severity Score[2‡]



‡Efficacy and safety assessments were performed by a trained evaluator at baseline, and at 12 and 24 hours post-baseline (N=57). Subjects (2-36 months of age) must have received an "Overall Severity Score" of >1.5 as determined by evaluator at enrollment. Diaper rash severity was assessed using a 0- to 3-point scale (0=none; 3.0=severe).

Proven formula

Contains the maximum amount of zinc oxide[3] in a petrolatum and cod liver oil formula base

40% zinc oxide

TREATS • PROTECTS • HEALS

Also recommend DESITIN® Rapid Relief Cream

For every diaper change, every day, and at the first signs of redness.

- Formulated to protect and help prevent recurrence—more spreadable for instant protection that lasts from diaper change to diaper change[1]
  - —**13% zinc oxide** in a mineral oil and petrolatum cream base provides an instant barrier to help seal out wetness and irritants

References: 1. Data on file. **2.** Brown WM, Berg JE, Li Q, Kohut BE. A clinical study to evaluate the efficacy of two marketed zinc oxide-based diaper rash ointments in children with diaper dermatitis. Poster presented at: Clinical Dermatology Conference; October 6-9, 2006; Las Vegas, NV. **3.** Product monograph. 68 FR 33377, June 4, 2003.

Use as directed.

#1 with Pediatricians and Moms.

Desitin®

The diaper rash experts.

inter@ctive

JOIN US AND JOIN IN WITH YOUR PEDIATRIC PEERS AT CONTEMPORARYPEDIATRICS.COM

MORE MOC TALK

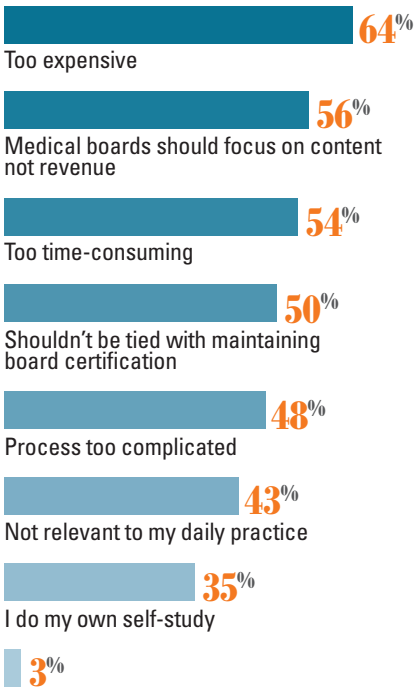
When it comes to the American Board of Pediatrics' Maintenance of Certification program, and specifically ABP's Dr. Virginia Moyer's recent column about it ("Maintenance of Certification: Myths, facts, and FAQs," August 2014) many of you had plenty to say in response! Here's just a sampling. See and say more online at bit.ly/1mRVqNy

"… the MOC process may have indeed preceded the 'disaster-that-is-Obamacare,' but it is, IN FACT, an extenuation of the current political/corporate trend to keep doctors in their place—totally subjugated to the 'suits and lawyers' … The powers-that-be are NOT hearing the boots-on-the-ground." *—Mary H. Johnson, MD*

"… Certification has NEVER been proven to cause improved care and these organizations continue to publish poorly conducted retrospective and BIASED 'science' much like this advertisement here … It is TIME for opportunity to publish opposing views and I look to this journal to live up to basic ethics and invite such a contra-point statement or sponsor a debate!" *—Paul M. Kempen, MD, PhD*

"I have faithfully maintained certification while trying to remain optimistic about MOC's stated purpose, but must agree with most of the responses to Dr. Moyer's article. It is true that no one ever expected doctors to be 'qualified' and current after passing one exam early in one's career, but that is what [CME] was supposed to achieve . . . A careful read of [the] article reveals that the Boards admit they have not achieved what MOC should achieve . . . That leaves us physicians where? With a far-from-optimal process that is expensive, time-consuming . . . and of unproven benefit … I have identified activities . . . that garner CME credits, and yet, this does not count toward my lifelong learning? The only reason I can think of is, the ABP wishes to monopolize MOC for their own gains." *— Colin K. Phoon, MD*

It's generally agreed that physicians need to keep current with new information and diagnostic and treatment guidelines, but the MOC process has been widely criticized. What, specifically, makes the MOC process so onerous?



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a response that's been proven

Count on PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

Protective efficacy demonstrated against *Haemophilus influenzae* type b in a high-risk population

Efficacy results at 15 to 18 months of age after primary 2-dose regimen (n=3,486)[a,b]

93% protective efficacy[c]
(95% CI, 57%–98%)

After additional follow-up of 2 years and 9 months[d]

97% protective efficacy[c]
(95% CI, 72%–99.9%)
in children under 18 months

100% protective efficacy[c]
(95% CI, 24%–100%)
in children over 18 months

[a]PedvaxHIB[e] was initially evaluated in a randomized, double-blind, placebo-controlled study of Native American (Navajo) infants (n=3,486). Each infant in this study received 2 doses of either placebo or lyophilized PedvaxHIB with the first dose administered at a mean of 8 weeks of age and the second administered approximately 2 months later; DTP and OPV were administered concomitantly; [b]Protective efficacy in such high-risk populations would be expected to be predictive of efficacy in other populations. A booster dose of PedvaxHIB is required in infants who complete the primary 2-dose regimen before 12 months of age. This booster dose will help maintain antibody levels during the first 2 years of life when children are at highest risk for invasive Hib disease; [c]Estimated from person-days at risk; [d]Subjects in this portion of the study received 1 to 3 doses of PedvaxHIB; [e]A lyophilized formulation was used in the study. A later study found the antibody response of Liquid PedvaxHIB to be comparable. The antibody responses induced by each formulation of PedvaxHIB were similar.

CI=confidence interval; DTP=diphtheria and tetanus toxoids and pertussis [vaccine]; OPV=oral polio vaccine; Hib=*Haemophilus influenzae* type b.

✔ **3-dose series can spare baby a shot[1]**

✔ **Ready to use—no need to reconstitute**

✔ **Discounted pricing may be available for PedvaxHIB. Speak to your Merck representative for more information**

Indication

PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age. PedvaxHIB should not be used in infants <6 weeks of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE.

PedvaxHIB is administered in a 2-dose primary regimen before 14 months of age. Infants 2 to 14 months of age should receive a 0.5 mL dose of vaccine, ideally beginning at 2 months of age, followed by a 0.5 mL dose 2 months later (or as soon as possible thereafter). When the primary 2-dose regimen is completed before 12 months of age, a booster dose (0.5 mL) should be administered at 12 to 15 months, but not earlier than 2 months after the second dose.

Select Safety Information

PedvaxHIB is contraindicated in patients with hypersensitivity to any component of the vaccine. Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

The most frequently reported (>1%) adverse reactions, without regard to causality, were fever (≥101°F), irritability, sleepiness, injection-site pain/soreness, injection-site erythema (≤2.5 cm diameter), injection-site swelling/induration (≤2.5 cm diameter), unusual high-pitched crying, prolonged crying (>4 hours), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

As with any vaccine, vaccination may not result in a protective antibody response in all individuals given the vaccine. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination.

Please see the adjacent Brief Summary of the Prescribing Information.

Reference: 1. Centers for Disease Control and Prevention. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States, 2013. http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf. Accessed February 19, 2013.

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PedvaxHIB®
[Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

INDICATIONS AND USAGE

Liquid PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

Liquid PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis. As with any vaccine, vaccination with Liquid PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine.

BECAUSE OF THE POTENTIAL FOR IMMUNE TOLERANCE, Liquid PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE. (See PRECAUTIONS in full Prescribing Information.)

Revaccination

Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION in full Prescribing Information).

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

PRECAUTIONS

General

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

As with other vaccines, Liquid PedvaxHIB may not induce protective antibody levels immediately following vaccination.

As reported with Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

There is insufficient evidence that Liquid PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccination should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.

If PedvaxHIB is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

Instructions to Healthcare Provider

The healthcare provider should determine the current health status and previous vaccination history of the vaccinee.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of PedvaxHIB or other Haemophilus b Conjugate Vaccines.

Information for Patients

The healthcare provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see ADVERSE REACTIONS in full Prescribing Information.

Patients, parents, and guardians should be instructed to report any serious adverse reactions to their healthcare provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB; in clinical studies with lyophilized PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Liquid PedvaxHIB has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older.

Pediatric Use

Safety and effectiveness in infants below the age of 2 months and in children 6 years of age and older have not been established. In addition, Liquid PedvaxHIB should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen). Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older because they are generally not at risk of Hib disease.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] with those of lyophilized PedvaxHIB, 1,699 doses of Liquid PedvaxHIB were administered to 678 healthy infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. Both formulations of PedvaxHIB were generally well tolerated and no serious vaccine-related adverse reactions were reported.

During a three-day period following primary vaccination with Liquid PedvaxHIB in these infants, the most frequently reported (>1%) adverse reactions, without regard to causality, excluding those shown in the table, in decreasing order of frequency, were: irritability, sleepiness, injection site pain/soreness, injection site erythema (≤2.5 cm diameter, see table), injection site swelling/induration (≤2.5 cm diameter, see table), unusual high-pitched crying, prolonged crying (>4 hr), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

Selected objective observations reported by parents over a 48-hour period in these infants following primary vaccination with Liquid PedvaxHIB are summarized in the following table.

Fever or Local Reactions in Subjects First Vaccinated at 2 to 6 Months of Age with Liquid PedvaxHIB[a]

Reaction	No. of Subjects Evaluated	Post-Dose 1 (hr)			No. of Subjects Evaluated	Post-Dose 2 (hr)		
		6	24	48		6	24	48
		Percentage				Percentage		
Fever[b] >38.3°C (≥101°F) Rectal	222	18.1	4.4	0.5	206	14.1	9.4	2.8
Erythema >2.5 cm diameter	674	2.2	1.0	0.5	562	1.6	1.1	0.4
Swelling >2.5 cm diameter	674	2.5	1.9	0.9	562	0.9	0.9	1.3

[a]DTP and OPV were administered concomitantly to most subjects.
[b]Fever was also measured by another method or reported as normal for an additional 345 infants after dose 1 and for an additional 249 infants after dose 2; however, these data are not included in this table.

Adverse reactions during a three-day period following administration of the booster dose were generally similar in type and frequency to those seen following primary vaccination.

Lyophilized PedvaxHIB

In The Protective Efficacy Study (see CLINICAL PHARMACOLOGY in full Prescribing Information), 4,459 healthy Navajo infants 6 to 12 weeks of age received lyophilized PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received lyophilized PedvaxHIB and those who received placebo, and none was reported to be related to lyophilized PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to lyophilized PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to lyophilized PedvaxHIB.

In early clinical studies involving the administration of 8,086 doses of lyophilized PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, lyophilized PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. In a subset of these infants, urticaria was reported in two children, and thrombocytopenia was seen in one child. A cause and effect relationship between these side effects and the vaccination has not been established.

Potential Adverse Reactions

The use of Haemophilus b Polysaccharide Vaccines and another Haemophilus b Conjugate Vaccine has been associated with the following additional adverse effects: early onset Hib disease and Guillain-Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.

Post-Marketing Adverse Reactions

The following additional adverse reactions have been reported with the use of the lyophilized and liquid formulations of PedvaxHIB:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skin

Sterile injection site abscess

For more detailed information, please read the full Prescribing Information.

Manufactured and distributed by: Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

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VACC-1072870-0000 03/13

A medical home far away from home

If the medical home concept of team-based healthcare works for kids and their families in Peru, it will work in your community, too.

Pediatricians know that coordination and advocacy work. What happens, however, when we are faced with complex cases in conditions that are nontraditional and prohibitively difficult? We all have faced these situations in practice in the United States. For our team, the problem came into sharper focus while working overseas.

The American Academy of Pediatrics' policy statement on the medical home states that "medical care of infants, children, and adolescents ideally should be accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective."[1]

M. Townsend Cooper Jr., MD, FAAP

We pediatricians strive to make this vision a reality for our patients in whatever environment we find ourselves practicing. Sometimes this involves case management in well-established clinics in tertiary care facilities. Sometimes it involves using a medical home model within a community-based practice. Sometimes, however, it calls for us to create a significantly different model. Although we must adjust our approach, the basic principles of coordinated, family-centered care remain constant.

Caring for medically fragile kids

What really makes a difference for medically fragile children in complex, resource-limited environments? This is the question that faces our team daily as we work in the sprawling, informal invasion settlements constantly springing up in the South American metropolis of Lima, Peru. We frequently find children living in extreme poverty with complicated disease courses (cerebral palsy, congenital heart disease, sequelae from injury) who are receiving substandard care. This is not only disastrous for them, but it also presents an economic and personal catastrophe for their families.

Wayne A. Centrone, NMD,MPH

What puzzled us most when we started working in these economically impoverished areas was the fact that reasonable-quality, appropriate care was often available at low or no cost within the government system, within just a few kilometers of where the children were living. We found ourselves asking, "Where is the breakdown? What can we do?" Duplication of services and resources was not the answer. This would neither improve efficiency nor enhance coordination with the local system. Reproduction of services was simply an unsustainable solution.

We realized that an unfortunate combination of poor (or no) care coordination, logistical barriers such as transportation, and lack of family education was creating an unhealthy synergy. This, in turn, was excluding some patients with complex illness from badly needed, government-subsidized care. Because of the lack of a few pieces of the puzzle, these patients were losing out on the whole package of meaningful care. Whether it was the child with cerebral palsy who could not access her tuberculosis care because of a lack of transportation, or a child with complex congenital heart disease who was not receiving care because of a lack of maternal job insecurity, these kids were missing out. In almost every case, the missing pieces cost a fraction of the children's overall state-subsidized care. Families lacking the small resources that

▲ **The SYNC project target community in Lima, Peru.**

would allow them to coordinate transportation, procure supplies, or gain support were missing out on many of the free services the state had to offer.

The fact that children with complicated illness have increased care utilization is well established in the literature.[2] What is lacking are well-defined models that can be applied in complex, resource-limited environments to better coordinate care for vulnerable children. The medical home model in North America has shown promise in improving overall care of medically complex children.[3] The nurse case management model also has been shown to be effective in improving care and reducing costs.[4] Community health promoter models have been used to improve the health of communities in a variety of ways and in both urban and rural settings.[5,6] Few of these models, however, have been tested in environments with such complex need and limited resources.

Our solution to the problem

In response to what we saw as a tragic and frustrating problem, we combined the medical home, the nurse case management, and the community health promoter approaches into a combined care-delivery model that we call the **S**eguimiento **Y** Coordinación Inter-profesional para **N**iños con **C**asos Complejos (SYNC) Project.

We created a team-based model comprised of health "ambassadors," a social worker, and a supervising nurse care coordinator.

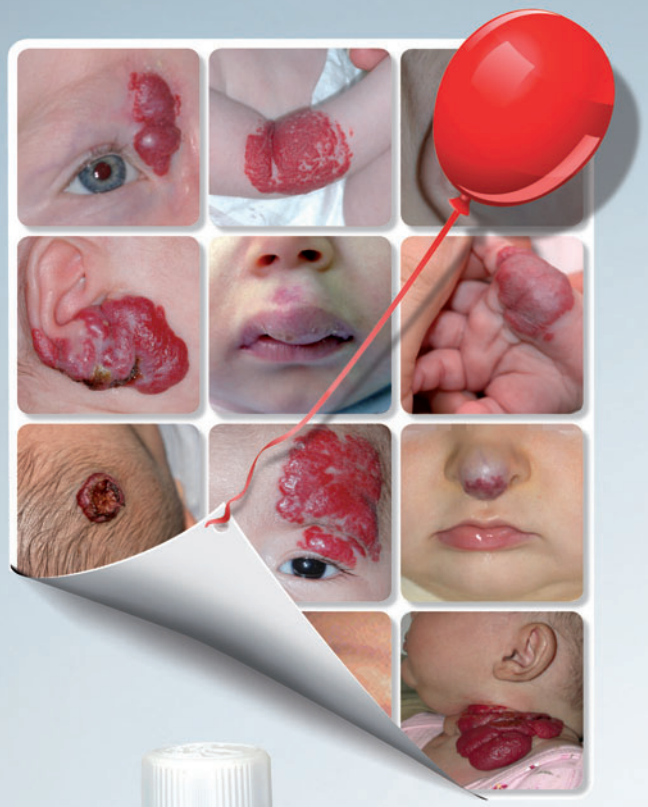
Our health ambassadors are members of the local communities, well versed in microculture, available resources, and the varied logistical challenges of the individual communities across the city. They are the backbone of the SYNC project, providing consistent interaction with the medically fragile patients and their families. A social worker helps with legal and system-level issues. The driving engine of the project is the nurse care coordinator. She provides targeted education, advocacy, and guidance for each patient and family. With her broad system knowledge and cultural competence, the nurse coordinator is able to target and fill the specific gaps in care delivery.

Using this team-based approach, along with limited resource interventions (eg, transportation costs, support for needed testing, and more), we keep children moving through the system who otherwise would fall through the cracks.

TO LEARN MORE ABOUT THE SYNC PROJECT and the Anglican Church of Peru's medical mission, visit www.peru.anglican.org/harvestMedical.html, or send e-mail to Dr. Cooper at townsendcooper@gmail.com. For information about Health Bridges International, visit http://hbint.org/ or contact Dr. Centrone at info@hbint.org.

Dr Cooper is director of medical projects, Anglican Church of Peru, Lima. **Dr Centrone** is executive director, Health Bridges International, Portland, Oregon, and vice president of research and design laboratory, Center for Social Innovation, Boston, Massachusetts. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in this article.

For an extended version of this article with references, go to **bit.ly/dispatches1014**



80% of hemangioma growth is complete at 3 months.[1]

Up to 69% of infantile hemangiomas leave residual lesions when left untreated.[2]

Proven efficacy

as shown in a phase II/III clinical trial.

60.4% of complete or nearly complete resolution by six months *versus* placebo 3.6%.

88% of patients showed improvement at week 5 of treatment.

Safety profile

The most common adverse reactions (occurring ≥10% of patients) were sleep disorders, aggraved respiratory tract infections, diarrhea, and vomiting.

Fewer than 2% of treated patients discontinued treatment due to safety concerns.

Hemangeol™

(propranolol hydrochloride) oral solution **4.28 mg/mL**

The only FDA approved drug for infantile hemangioma

There is no therapeutically equivalent drug.

Indication

Hemangeol™ (propranolol hydrochloride) is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

MANAGE EARLY*

*Initiate treatment at ages 5 weeks to 5 months.

1. Tollefson M & Frieden IJ. Pediatrics 2012;130:e314.
2. Bauland CG et al. Plast Reconstr Sur. 2011;12:1643–8.

See important safety information on the adjacent page.

HEM-14279A

Pierre Fabre Pharmaceuticals, Inc.

Pierre Fabre DERMATOLOGIE

Important safety information

Hemangeol™ (propranolol hydrochloride) oral solution is contraindicated in the following conditions: • Premature infants with corrected age <5 weeks • Infants weighing less than 2 kg • Known hypersensitivity to propranolol or any of the excipients • Asthma or history of bronchospasm • Heart rate <80 beats per minute, greater than first degree heart block, or decompensated heart failure • Blood pressure <50/30 mmHg • Pheochromocytoma.

Hemangeol™ prevents the response of endogenous catecholamines to correct hypoglycemia and masks the adrenergic warning signs of hypoglycemia, particularly tachycardia, palpitations and sweating. Hemangeol™ can cause hypoglycemia in children, especially when they are not feeding regularly or are vomiting; withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. If a child has clinical signs of hypoglycemia, parents should discontinue Hemangeol™ and call their health care provider immediately or take the child to the emergency room.

Concomitant treatment with corticosteroids may increase the risks of hypoglycemia. Hemangeol™ may cause or worsen bradycardia or hypotension. Monitor heart rate and blood pressure after treatment initiation or increase in dose. Discontinue treatment if severe (<80 beats per minute) or symptomatic bradycardia or hypotension (systolic blood pressure <50 mmHg) occurs.

Hemangeol™ can cause bronchospasm; do not use in patients with asthma or a history of bronchospasm. Interrupt treatment in the event of a lower respiratory tract infection associated with dyspnea and wheezing.

Hemangeol™ may worsen circulatory function in patients with congestive heart failure or increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Investigate infants with large facial infantile hemangioma for potential arteriopathy associated with PHACE syndrome prior to Hemangeol™ therapy.

Hemangeol™ will interfere with epinephrine used to treat serious anaphylaxis.

The most frequently reported adverse reactions to Hemangeol™ (occurring ≥10% of patients) were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting. Adverse reactions led to treatment discontinuation in fewer than 2% of treated patients.

The most common (>3% more often on Hemangeol™ than on placebo) adverse reactions reported in a total of 424 patients treated with Hemangeol™ 1.2 mg/kg/day or 3.4 mg/kg/day were sleep disorder (17.5%; 16.1%), bronchitis (8%; 13.4%), peripheral coldness (8%; 6.7%), agitation (8.5%; 4.5%), diarrhea (4.5%; 6.3%), somnolence (5%; 0.9%), nightmare (2%; 6.3%), irritability (5.5%; 1.3%), decreased appetite (2.5%; 3.6%), and abdominal pain (3.5%; 0.4%), respectively.

Adverse events such as cardiac disorders, urticaria, alopecia, decreased blood glucose, and decreased heart rate occurred in less than 1%.

Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than 1 year of age.

Indication

Hemangeol™ is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

Please see Full Prescribing Information on www.hemangeol.com

HEM-14279A

Adverse effects of montelukast examined by FDA's Pediatric Advisory Committee

Members vote for clearer warning labels advising physicians about risks of neuropsychiatric events.

At its late September meeting, the Pediatric Advisory Committee (PAC) to the US Food and Drug Administration (FDA) said it's time to remind healthcare professionals that Singulair (montelukast) may have adverse effects on mental and behavioral functions.

The 13-member committee called for clarifications on labels and for a new letter to providers, even though the association to such conditions has not been proven, warnings are on the labels, and a letter has gone out previously.

Montelukast is used most often in association with diagnoses of asthma and allergies in children, according to the FDA.

The FDA's "Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review," made available for the meeting, said, "Safety concerns have been raised and addressed by the FDA in the past regarding the increased risk of neuropsychiatric adverse events, including suicide and suicide attempts with the use of montelukast. However, there continues to be a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among patients using montelukast."

Concerns with montelukast

Over about 18 months ending in September 2013, almost 9 million patients received dispensed prescriptions for the drug from outpatient retail pharmacies. Thirty-eight percent of those patients were aged 16 years or younger, according to the FDA's review.

The agency said its Adverse Event Reporting System found 140 pediatric serious cases for montelukast, including 4 deaths, during that same time frame ending in September 2013, and neuropsychiatric events were reported for the majority of those cases.

The public testimony phase of the meeting heard from Jan Gilpin, a member of the group Parents United for Pharmaceutical Safety and Accountability, formed in 2009 over concerns that children had developed mental and development issues while on montelukast. Her group and similar ones have hundreds of members, she said. Years ago, she testified, her son developed crippling anxiety while taking the drug and said he wished that he were dead.

Committee members noted that although some of the reports the FDA had gathered indicated relatively acute onset of problems in children, the rates for those conditions are also higher in all children with chronic medical problems including asthma.

PAC calls for clarity in labeling

Kenneth Towbin, MD, chair of the PAC and chief of clinical child and adolescent psychiatry at the National Institute of Mental Health, said there was a uniform wish among committee members for a way to get better information about the frequency of those events, although the committee had no recommendation on how to do that. He said the National Institutes of Health might be the place to think about the problem.

Googling on cell phones in the midst of the discussion, committee members got a different listing of precautions for the drug from reputable medical information sites, but there were references to possible mental effects on several of them.

The committee voted to recommend that the professional label should have the same kind of clarity as the consumer labeling; that the consumer labeling should have the reference to mental effects easier to see and higher in the list of things to be aware of; and that a letter should be sent to make healthcare providers aware of these changes.

Robert (Skip) Nelson, MD, PhD, deputy director of the FDA Office of Pediatric Therapeutics, said the FDA has jurisdiction over safety labeling. "We can work out what authority we have, but we will make every effort to do it," he said.

The FDA Division of Pharmacovigilance recommended that it continue surveillance on adverse events and the committee agreed.

In May, the FDA Nonprescription Drugs Advisory Committee recommended that the FDA not allow Singulair to be sold over the counter because of fear that persons would not use it wisely.

During the September pediatric meeting, the committee also agreed with the FDA's recommendations that it continue surveillance for adverse events for about 11 other pediatric drugs and devices.

The labeling and review information is on the FDA's web page for the September 23, 2014, PAC meeting. ■

Teen birth rates still declining

Birth rates for adolescents in the United States continue their dramatic drop, although they are still far higher than in most developed countries, according to a report issued by the National Center for Health Statistics (NCHS).

Last year, adolescent girls aged 15 to 19 years had a birth rate of 26.6 births per 1000, according to preliminary data—less than half the 1991 rate of 61.8 and less than one-third the 1957 rate of 96.3.

The decline has been almost continuous for 5 decades except for small upturns and a 23% increase from 1986 to 1991. The 2013 total number of adolescent births, at 274,641, was below 300,000 for only the second time since 1940. Births numbered 280,997 in 1945 and peaked at 644,708 in 1970.

However, the United States, which long had the highest teenaged birth rate of all developed countries, still has one of the highest. Switzerland had a recent rate of 3.4 and the Netherlands had a rate of 4.8. Of 31 selected countries including Japan, Canada, Israel, and many European nations, only 7 had rates above 20 in reports from 2009-2012.

The vast majority of adolescent births in the United States are to mothers aged 18 or 19 years. In 2013, that group had 199,407 births; girls aged 15 to 17 years had 75,234; and those aged 10 to 14 years had 3108.

Although almost all states have seen impressive reductions in the last 20 years, states still vary greatly both in their adolescent birth rates and in the rates of decline. In 2012, Vermont had an adolescent birth rate of 16.3 per 1000 for teenagers aged 15 to 19 years and New Hampshire's rate was 13.8. On the other end of the scale, New Mexico's rate was 47.5 and Oklahoma's was 47.3.

States with rates of 36 or higher per 1000 were Alabama, Arizona, Arkansas, District of Columbia, Kentucky, Louisiana, Mississippi, New Mexico, Oklahoma, South Carolina, Tennessee, Texas, and West Virginia.

The lowest teenaged birth rates, 13.8 to 22.9, were in Connecticut, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Rhode Island, Vermont, Virginia, and Wisconsin.

The NCHS says the drop in the adolescent birth rate during 2007-2012 ranged from 18% in Montana to 39% in Colorado.

Colorado has received media attention on its rapid reduction, attributed to the Colorado Family Planning Initiative they say has provided 30,000 intrauterine devices or implants free or inexpensively to low-income women at 68 family planning clinics since 2009. According to a report in the September *Perspectives on Sexual and Reproductive Health*, beginning in 2009, 28 Title-X funded agencies in Colorado got private funding for the initiative and by 2011 long-acting reversible contraceptive use "among 15–24-year-olds had grown from 5% to 19%."

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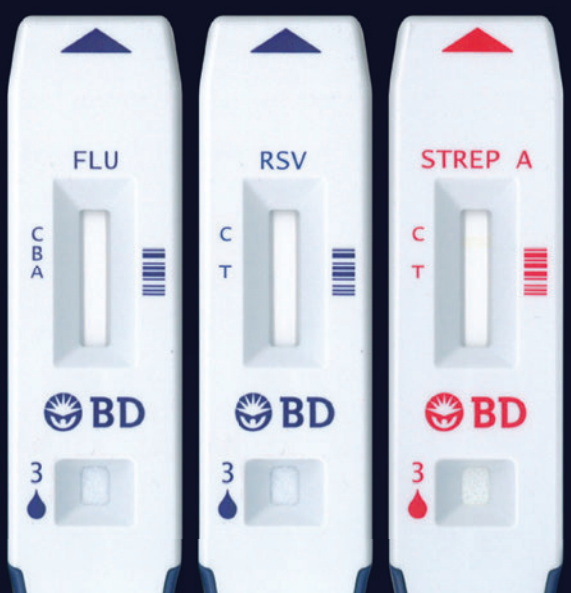

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References: 1. Data on File.

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BY MARIAN FREEDMAN | COMMENTARY BY MICHAEL G BURKE, MD | f CONTEMPORARYPEDIATRICS

Parental supervision enhances adolescents' prelicense driving skills

A web-based program that guides parents in supervising their children's practice drives with focus on specific skills in a variety of driving environments improves driving performance in prelicensed 16- and 17-year-olds, a trial of such a program showed.

Investigators in southeastern Pennsylvania divided 217 parent-teenager twosomes into 2 groups. One group was enrolled in the Teen Driving Plan (TDP), which provides 53 brief videos for parental supervision on structuring practice drives to focus on particular driving skills, along with components such as phone calls, to increase parental engagement in providing effective supervision and social support to their children as they develop their driving skills. Program materials for the TDP group were divided into 6 different driving environments: empty parking lots; suburban residential streets; 1- or 2-lane roads; highways; rural roads with curves and elevation changes; and commercial districts.

The second (control) group received a copy of the Pennsylvania driver's manual, which also was available to families in the TDP group but not provided to them.

At 24 weeks after study enrollment, families in the TDP group reported more practice in each of the 6 environments (except for highways) and after dark as well as in bad weather than those in the control group. The additional practice was reflected in results of a challenging on-road driving assessment across the 6 environments. Professional driving evaluators administered the test to teenaged participants in both groups, terminating it if they determined that the adolescent could not complete the test safely. Overall, evaluators terminated the test in 6% of the TDP group compared with 15% of the control group (Mirman JH, et al. *JAMA Pediatr.* 2014;168[8]:764-771).

commentary

This makes sense. Who can say that the supervising parent of a new driver is going to be a good driver or a good teacher? As described, the TDP program offers information and structure to the parent who takes on the role of teaching an adolescent to drive, increasing the likelihood that the child will get his or her license. I suspect that the program also results in a better-trained teenaged driver, leading to reduced risk of early accidents and less-stressed parents.
—Michael G Burke, MD

Antiviral compound shows promise as therapy for RSV

The oral respiratory syncytial virus (RSV) entry inhibitor GS-5806 reduces both viral load and clinical manifestations of RSV infection, according to results of a trial in which investigators infected healthy adults with a nasally delivered clinical strain of RSV.

Researchers administered the small-molecule antiviral agent or placebo to 140 participants (aged 18 to 45 years) either when they tested positive for RSV infection or 5 days after inoculation with RSV, whichever occurred first. The antiviral agent was administered to 7 sequential groups under varied dose and dosing regimens.

Compared with participants

who received placebo, those given GS-5806 had a lower mean viral load as measured by the area under the curve, assessed after administration of the first dose through the 12th day after inoculation. In addition, mean total weight of mucus and mean change from baseline in total symptom scores (based on participants' diaries) were lower for those who received GS-5806 than for those who received placebo.

Although no serious adverse events occurred during the trial, mild or moderate adverse events, including low neutrophil counts and increased levels of alanine aminotransferase, were more common among participants receiving GS-5806 (DeVincenzo JP, et al. *N Engl J Med*. 2014;371[8]:711-722).

commentary

This could turn out to be an exciting pharmacologic development. Respiratory syncytial virus continues to be the most common reason for infant hospitalization in the United States. Despite loads of studies and proposed approaches, we are left with nothing much to offer but supportive care. Many questions still need to be answered. Is the medication effective in children, and specifically in infants with RSV? Are the adverse effects different in children? Which patients would benefit from this therapy? Would it affect the likelihood of childhood wheezing after RSV? Finally, what would be the cost? With these questions and the long investigative road ahead, this could be big news for treatment of RSV in children. —Michael G Burke, MD

Sickle cell anemia raises risk for obstructive sleep apnea syndrome

Children with sickle cell anemia (SCA) are more likely to have obstructive sleep apnea syndrome (OSAS) than the general pediatric population, with habitual snoring and low waking pulse oxygen saturation the strongest risk factors for developing the condition. Other risk factors for OSAS in these children revealed by a recent study were reduced lung function, less caretaker education, and non–preterm birth.

These were the major findings from the Sleep and Asthma Cohort Study, which evaluates the contribution of sleep and breathing abnormalities to SCA-related morbidity in youngsters aged 4 to 18 years. Investigators determined OSAS status from overnight polysomnography and the presence of generally accepted risk factors, as indicated on parental questionnaires and from direct measurements.

The 243 study participants (median age, 10 years) were recruited from pediatric centers in 3 cities, and the vast majority were of African heritage and homozygous for sickle cell hemoglobin. Obstructive sleep apnea syndrome was present in 41% or 10% of participants, depending on the obstructive apnea hypopnea index (OAHI) cutoff points used. Frequency of habitual snoring, trouble breathing, witnessed apnea, and nocturnal enuresis increased with OAHI values; nocturnal restlessness or daytime sleepiness did not (Rosen CL, et al. *Pediatrics*. 2014;134[2]:273-281).

commentary

We now have good evidence that children with SCA have a high risk of silent cerebral infarcts. Vascular endothelial changes seem to explain these risks. However, I wonder if hypoxia from unrecognized obstructive sleep apnea contributes to this complication. A history of habitual snoring or documentation of a low waking pulse oximetry measurement may be enough to trigger a sleep study in these patients. —Michael G Burke, MD

also of note

To aid teenagers' compliance, try text message reminders. A study of the use of text messaging to aid an investigation in adolescents requiring the regular collection of urine samples found a high response rate to text message reminders, resulting in missed collections of less than 10%. This suggests that text messaging is an acceptable and feasible tool for reminding teenagers about appointments, medications—whatever (Balzer BW, et al. *Arch Dis Child*. 2014;99[7]:666-667).

puzzler

Boy's lymphadenopathy leads to acute heart failure

NATALIE DARRO, DO, PGY3; CHRISTOPHER MURRAY, MD; PISESPONG PATAMASUCON, MD

THE CASE

You are the night float senior on inpatient hospital service when you receive a transfer from an outside hospital of a 5-year-old Hispanic male who presented with 2 days of fever, unilateral neck swelling with torticollis, and neck pain.

Two weeks prior to admission, the patient had upper respiratory symptoms that had been resolving until 2 days before admission, at which point he developed headache and fatigue. His parents reported a tactile fever and 2 episodes of nonbloody, nonbilious vomiting. On the day before admission, the patient awoke with increasing neck pain and a small bump on the right side of his neck.

Evaluation by the boy's primary care physician (PCP) was significant for fever (105°F). Based on suspected lymphadenitis, the PCP ordered several laboratory tests and started the patient on cefdinir. The following day, the patient was again febrile (102°F) and had poor oral intake, increasing pain, and severely decreased mobility of his neck with increased swelling. The child was taken to the emergency department (ED) at this time.

In the ED, the patient was febrile (100.6°F) and tachycardic but in no acute distress, and he had stable respirations. He had laboratories drawn and underwent a computed tomography (CT) scan with contrast of the neck, which revealed right-sided lymphadenitis, no abscess formation, no separation, and a lymph node (LN) enlarged to 2.7 cm. He was treated with a 20 mL/kg normal saline bolus, intravenous (IV) clindamycin, dexamethasone IV, oral acetaminophen, and ibuprofen. He was then transferred to your hospital.

On review of systems upon arrival, the patient's family denied exposure to cats or other animals at home or exposure to populations at high risk for tuberculosis. The boy had never traveled outside the United States. Over the summer, he did have contact with farm animals at a petting zoo. He had never been hospitalized before or experienced skin infections. The family reported no rashes; swelling in locations other than the neck; swelling of hands or feet; redness of mucus membranes or eyes; diarrhea; or difficulty with urination, although decreased urination secondary to poor oral intake was observed during the previous 2 days.

Birth history was benign and there was no pertinent past medical or surgical history. However, the family history was notable for obesity and type 2 diabetes mellitus.

Physical examination

Evaluation upon arrival to the pediatric floor reveals an obese 5-year-old male who appears to be in no acute distress and who is interactive with no appearance of toxicity. Temperature is normal (98.1°F) as is oxygen saturation (98%). However, heart rate and blood pressure are elevated

TURN TO PAGE 41 FOR MORE CLUES ▶

Cystic fibrosis
An essential update

MICHAEL S SCHECHTER, MD, MPH.
MEDICAL WRITING SUPPORT PROVIDED BY CRYSTAL MURCIA, PHD.

Dr Schechter is professor of pediatrics, Virginia Commonwealth University (VCU), and chief, Division of Pulmonary Medicine, Children's Hospital of Richmond at VCU, Richmond, Virginia. He discloses research support from Vertex Pharmaceuticals and Novartis, and consulting for Vertex, Gilead Sciences, Novartis, Genentech, and Celtaxsys. In addition, he has served on data safety monitoring committees for AstraZeneca and Bayer.

Working in concert with families and cystic fibrosis (CF) care centers, pediatricians can play a vital role in ensuring the continued success of strategies for managing CF and its affiliated conditions in children.

The prognosis for patients with cystic fibrosis (CF) continues to improve because of a combination of advances in the understanding of disease pathophysiology, implementation of early screening and diagnosis, and greater emphasis on proactive management to prevent deterioration and disease progression.

Cystic fibrosis is the most common life-shortening genetic disease among Caucasians, who represent 94% of the CF population in the United States.[1] The probability of a Caucasian child being born with CF is approximately 1 in 2500.[2] By comparison, the likelihood of CF in the Hispanic American and African American populations are 1 in 13,500 and 1 in 15,100 live births, respectively. It is estimated that there are currently 70,000 individuals living with CF worldwide, 30,000 of whom reside in the United States.[1] Children account for more than half of the CF population. The number of affected Americans continues to increase as new cases are diagnosed (approximately 1000 per year) and improvements in treatment and diagnosis enhance longevity. Indeed, within the past 20 years, the predicted median survival age for patients with CF has increased by more than 10 years (Table 1).[1]

Cystic fibrosis is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The CFTR protein was first classified as a chloride channel, but has subsequently been shown to facilitate or regulate the transport of other ions, such as sodium (through the epithelial sodium channel), thiocyanate, and bicarbonate.[3,4] The CFTR protein is present in the epithelia of various tissues including that of the lungs, sweat glands, gastrointestinal tract, vas deferens, and pancreas, where it helps regulate salt and water absorption and excretion.[5]

Disease-causing mutations in the *CFTR*

TABLE 1 SHIFTING DEMOGRAPHICS OF CYSTIC FIBROSIS

	1992	2002	2012
Median age at diagnosis	6 mo	6 mo	4 mo
Age range	0-71.0 yr	0-75.8 yr	0-82.7 yr
Predicted median survival	29.4 yr	31.3 yr	41.1 yr

Median values are presented for age at diagnosis.
Cystic Fibrosis Foundation.[1]

gene impede protein production, stability, or activity, resulting in less available functional protein.[4] In the lung, the ensuing perturbations in ion transport cause airway surface liquid depletion resulting in defective mucociliary clearance. Added to this is an abnormal inflammatory response, whose relation to the ion transport abnormality is unclear. Together, these physiologic changes lead to an iterative cascade of obstruction, inflammation, infection, and, ultimately, progressive, irreversible lung damage.[3]

Other manifestations of dysfunctional CFTR include pancreatic insufficiency resulting from ductal obstruction, meconium ileus because of increased viscosity of intestinal mucus, and congenital bilateral absence of the vas deferens (CBAVD) caused by obstruction of the Wolffian ducts during fetal development.[5,6] The influence of *CFTR* mutations on nonrespiratory organ systems affects growth, nutritional status, and fertility, but it is the lung disease that is predominantly responsible for CF-related morbidity and mortality.[7]

Newborn screening

One of the keys to improvements in CF outcomes has been the increasing adoption of a proactive approach to care, which includes the broad implementation of newborn screening (NBS). According to data from the Cystic Fibrosis Foundation Patient Registry, more than 61% of CF diagnoses in the United States in 2012 were made through NBS.[1] The rationale for instituting NBS programs is to mitigate the negative impact of untreated CF on lung structure and function and to prevent nutritional deterioration by providing appropriate monitoring and treatment.

It has long been known that infants with pancreatic insufficiency due to CF demonstrate poor growth and inadequate weight gain. Researchers are now beginning to appreciate that structural changes of the lungs have already begun to manifest within the first year of life in affected individuals.[8,9] Lung disease is generally not clinically apparent at these early stages because these nascent structural and physiologic abnormalities (eg, bronchial dilatation, bronchial wall thickening, gas trapping) and bacterial infections are usually asymptomatic during infancy.[8]

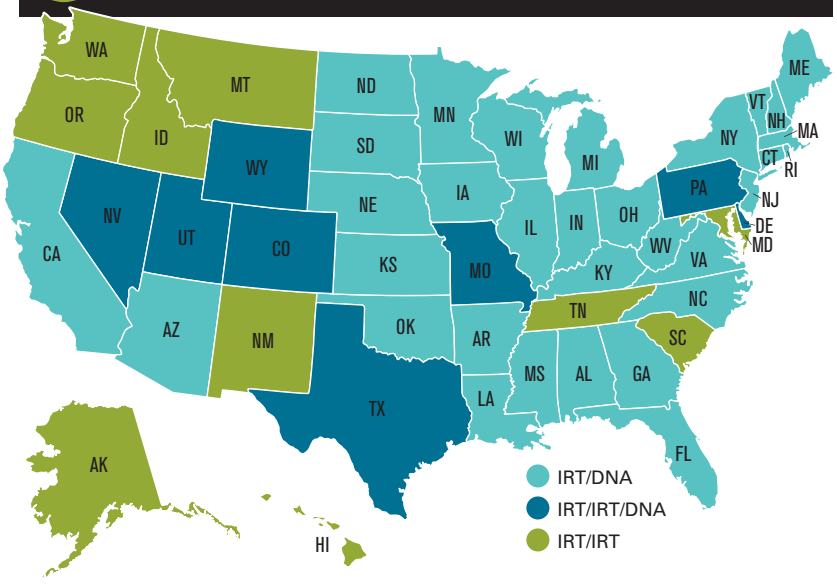
FAST FACT
The probability of a Caucasian child being born with cystic fibrosis is approximately 1 in 2500.[2]

Identification of patients through NBS has been associated with improved nutritional status, better cognitive function, improved pulmonary status/lung function, and fewer hospitalizations.[10-14] Newborn screening also has the potential to decrease the risk of life-threatening complications and death in infancy, and to reduce treatment costs.[7,15] Indeed, comparisons with historical data indicate an increased probability of survival into early adulthood for those diagnosed as the result of NBS.[12] For parents, the expedited time to diagnosis reduces distress and provides opportunities for genetic counseling, which could influence future childbearing decisions.[7]

Screening for CF is currently offered as a component of NBS programs in all 50 states. The CF screening programs are a multistep process that begins with the measurement of immunoreactive trypsinogen (IRT) levels in blood taken from the newborn heel prick. This pancreas-derived enzyme is typically elevated in all patients with CF, even those who are pancreatic sufficient. However, levels in the normal range may be present in infants with CF who present with meconium ileus.[10]

Meconium ileus is the first symptom of CF in approximately 15% to 20% of affected newborns.[7] Given the association with CF, it is recommended that all newborns who have meconium ileus (or any small bowel obstruction, even if it is not clearly recognized as meconium ileus) are administered a sweat test regardless

FIGURE 1 NEWBORN SCREENING FOR CF BY STATE



Missouri and Pennsylvania use a combination of IRT/DNA and IRT/IRT/DNA screening.

Abbreviation: CF, cystic fibrosis; DNA, deoxyribonucleic acid; IRT, immunoreactive trypsinogen.
From Cystic Fibrosis Foundation.[16]

of findings on the IRT screen.[10] Elevations in IRT that are not associated with CF may be detected in infants who experience perinatal stress or who have a low birth weight. African American infants may also demonstrate elevated IRT levels compared with Caucasian infants, which could result in a false-positive NBS.

The method for further assessment after finding an elevated IRT varies by state (Figure 1).[16] There are 4 NBS methods used in the United States. The most widely used approach, IRT/DNA, begins with IRT measurement when the infant is 1 or 2 days old. If the IRT level on the initial bloodspot is elevated (eg, in the 96th percentile), that same blood spot is tested for *CFTR* mutations from a predefined panel of the most common mutations. If even 1 mutation is found, the infant is referred for sweat testing, because no panel includes all mutations.

The second most common approach is IRT/IRT, for which the IRT assay is performed on blood specimens collected at age 1 to 2 days, then repeated again at approximately 2 weeks of age. Two elevated IRTs constitute a positive NBS for CF and indicate that a sweat test needs to be performed. A third approach, IRT/IRT/DNA, uses slightly lower thresholds for the IRT cutoff compared with the IRT/IRT method, but then checks the blood of children with 2 elevated IRT measurements for common *CFTR* mutations. Finally, the state of California uses a variation on the IRT/DNA approach in which gene sequencing rather than a screening panel is used when an elevated IRT is found, eliminating the role of sweat testing as a confirmatory test.

In all states other than California, the definitive diagnosis is made through sweat testing. Sweat collection is performed using pilocarpine iontophoresis and followed by measurement of chloride levels. This noninvasive procedure can be reliably performed once the infant reaches 72 hours of age. It should be noted that infants who are premature, weigh less than 2 kg, or who are African American have a higher likelihood of producing insufficient quantities of sweat for testing.[10]

A sweat chloride value of 60 mEq/L or greater is considered diagnostic for CF.[10,17] A result of 30 to 59 mEq/L is indeterminate but is often due to the presence of a *CFTR* mutation that has residual chloride channel function.[17] Beyond the age of 6 months, the indeterminate range for sweat chloride is 40 to 59 mEq/L. Patients with an indeterminate test result should undergo periodic retesting until test results are unequivocal or the presence of symptoms solidifies the diagnosis. Sweat testing should be performed at an accredited CF care center in order to be considered reliable. Cystic fibrosis care centers are supported by the Cystic Fibrosis Foundation and offer specialized care for children and/or adults with CF. A complete listing of CF care centers is available through the foundation's website.

For an extended version of this article with references, go to **bit.ly/CFupdate**

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Managing eczema

Pediatric atopic dermatitis experts share perspectives on how best to relieve symptoms of this common skin disease.

LISETTE HILTON

dematology special report

Prevalence of atopic dermatitis is on the rise, ranging from 10% to 20% in the United States and other developed countries.[1]

However, managing the severity of atopic dermatitis is no easy task. Flares come and go, and the reasons for uncomfortable exacerbations can be complex and hard to pinpoint. Making treatment more challenging is "steroid phobia," also known as "corticosteroid phobia," a concern many parents and others share about the safety of topical corticosteroids, the mainstay treatment for children with moderate to severe disease.[2]

Finding the best ways in which to manage patients with atopic dermatitis is critical, not only to relieve physical symptoms of the disease, but also to mitigate the psychosocial impact on children's and families' lives, according to Amy Paller, MD, professor and chair of dermatology and professor of pediatrics at Northwestern University Feinberg School of Medicine, Chicago, Illinois.

"We've always known that there are severe psychosocial effects.[3] [These range] from the highly visible lesions to the fact that these children don't sleep well, if they sleep. It's difficult in school because they're falling asleep and that makes them different. They have attentional issues at school. They don't feel comfortable playing or doing sports because they're so much itchier when they get hot," Paller says. "There are also neurocognitive issues with atopic dermatitis."

Quality of life is profoundly affected in children with moderate to severe disease, according to Paller.[4] "[T]he quality of life reported [by these kids] is [similar to] what we see with many of the chronic diseases, such as diabetes and seizures," she says.

Increasing understanding

Lawrence F. Eichenfield, MD, chief of pediatric dermatology and professor of pediatrics and medicine (dermatology)

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References: 1. Scalabrin DMF et al. *J Pediatr Gastroenterol Nutr.* 2012;54:343-352. **2.** Ashley C et al. *Nutr J.* 2012;11:38. doi: 10.1186/1475-2891-11-38. **3.** Ziegler E et al. *J Pediatr Gastroenterol Nutr.* 2007;44:359-364. **4.** Nakamura N et al. *Appl Environ Microbiol.* 2009;75:1121-1128.

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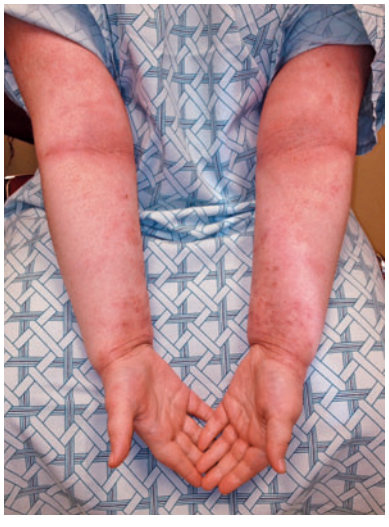
at the University of California, San Diego, and Rady Children's Hospital San Diego, California, says that atopic dermatitis advances and research have improved understanding of the epidemiology and pathogenesis of the disease.

"Over the last several years, identification of mutations in the skin responsible for skin barrier dysfunction, associated with the dry skin of eczema, as well as a setup for its inflammation, have been emphasized," says Eichenfield, an author on the atopic dermatitis guidelines released in 2014 by the American Academy of Dermatology.

Lawrence F. Eichenfield, MD

"Research has shown there are mutations in certain genes expressed in the epidermis that fundamentally influence the skin barrier function. Filaggrin gene mutations have been shown to have a strong predictive value for higher risk of development of atopic dermatitis, as well as increased rates of asthma, allergic rhinitis, [immunoglobulin E] sensitization, as well as more severe atopic dermatitis that can persist into late childhood and adulthood," he says.



▲ Good skin care and moisturizers can help minimize the impact of AD.

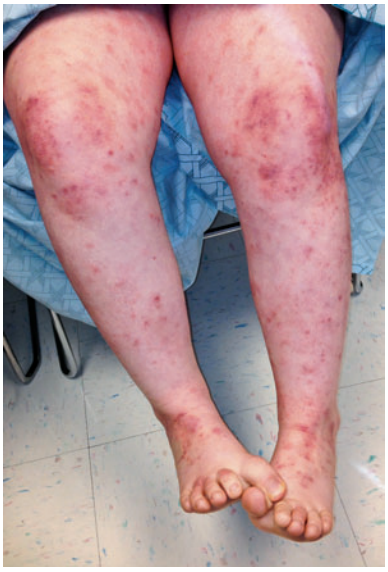
Eczema is a phenotype. Classic atopic dermatitis usually starts in early childhood. Whether adult onset atopic dermatitis is the same or a different disease is unclear, according to Elaine C. Siegfried, MD, professor of pediatrics and dermatology, Saint Louis University, Missouri. Also, the jury is still out on whether atopic dermatitis is a primary inflammatory disease or a primary barrier disease, she says.

"The pathogenesis is likely related to dysfunction in both systems. For some, it's probably primary inflammatory and for other people it's probably primary barrier," Siegfried says, "but the role of the cutaneous microbiome is being increasingly recognized as an important co-factor for both skin barrier and immune function."

From a clinical standpoint, the knowledge about skin barrier dysfunction reassures physicians that an approach emphasizing good skin care and liberal use of moisturizers can help to minimize the impact of the disease, according to Eichenfield.

Elaine C. Siegfried, MD

Infection can occur with atopic flares, but antibiotics are better left to treat skin infections, rather than try to prevent them, says Eichenfield. "Generally, in nonaffected atopic dermatitis the broad use of antibiotics is not recommended. However, infected eczema might benefit from systemic treatments," he says.



▲ Classic atopic dermatis usually begins in early childhood.

Treatment options still limited

The biggest breakthrough in atopic dermatitis treatment has been the development of topical corticosteroids, according to Siegfried. "Before [topical corticosteroids], treatment was incredibly difficult. After topical corticosteroids were developed, acute relief was possible for the majority of patients," she says.

However, long-term use of topical corticosteroid monotherapy carries the risk of adverse effects. Potential problems include cyclic rebound of the skin disease, cutaneous atrophy, and corticosteroid contact allergy.

"That's why steroid-sparing alternatives have been developed," Siegfried says, "and it's wonderful to have those options. The most well-studied are the topical calcineurin inhibitors Elidel and Protopic."

AUTHOR SUPPLIED

The public's phobia surrounding topical corticosteroid use, however, is more fear based than research based, according to Siegfried.

The perceived dangers of topical corticosteroids often lead to noncompliance. According to research published in October 2011 in the *British Journal of Dermatology*, parents and adult patients with atopic dermatitis who were surveyed reported fearing topical corticosteroids and more than a third admitted nonadherence to treatment.[5]

"You can overuse corticosteroids, but if you don't use them at all it can be very difficult to keep the disease under control," Siegfried says. "In my practice . . . corticosteroids are always first line. They're the most well studied and have been around for the longest period of time. [I]n people whose disease can't be controlled on a safe amount of corticosteroids, you have to add a steroid-sparing agent. Options include a calcineurin inhibitor or phototherapy. Some people still use tar, although most patients don't like it and there's a concern about carcinogenicity."

Calcineurin inhibitors are safe, well tolerated, and readily available, notes Siegfried.

Ms Hilton is a medical writer who has covered health and medicine for 25 years. She resides in Boca Raton, Florida. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

Find more eczema treatments at **bit.ly/managing-AD**

ALTERNATIVE TREATMENTS FOR ECZEMA

editor's note This article was previously published online in our sister publication *Dermatology Times*, September 19, 2014.

Eczema patients and their families often come to Peter Lio, MD, assistant professor of clinical dermatology and pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, and director of the Chicago Integrative Eczema Center, looking for relief through alternative treatments.

Peter Lio, MD

"Sometimes people come in and say, 'I don't want to use any Western medicine,'" he relates, "and I'll say, if it's the mildest eczema, perhaps we can get by. But for anything more severe, we really need to do this as part of a plan with the hopes of minimizing the amount of more powerful medicines by strengthening the skin and doing these other good things."

Here are some of the remedies his patients suggest with Dr. Lio's corresponding thumbs up, jury's out, and thumbs down determinations on them.

THUMBS UP

1. Sunflower seed oil

(Lio's favorite)

"It comes in a number of different forms. There are some products that have it built in. There are some bath oils that have it. I'm happy with any of those, but I really like just the pure sunflower seed oil," he says. Apply it to damp skin, twice a day. Sunflower seed oil naturally boosts the skin barrier function and has anti-inflammatory properties.

There is no downside to using it, the dermatologist says. "There is a theoretical risk that putting things on the skin that we eat can potentially make us allergic to them, but it does not appear to be a significant risk with sunflower seed oil, in my experience. If someone has a known allergy to sunflower seeds, however, then I would definitely avoid it," he says.

2. Coconut oil

People can buy it off the shelf, but should make sure it's virgin or cold-pressed coconut oil. Why? There might be residues of extraction chemicals in other coconut oil types.

Apply it once or twice a day to damp skin, if possible. Coconut oil has been shown to reduce staph bacteria on the skin and it acts as an emollient, according to Lio.

How about kids with nut allergies? "Coconut is a distant cousin of tree nuts. Some allergists put it in that group. It's a rare allergen, but certainly avoid it if you're allergic to coconuts," Lio says.

3. Acupressure

Lio uses just 1 acupressure point and has found it makes a difference for his patients. Patients or parents can apply the pressure at home, once they learn how, he says. "Some say that it is simply working as a distraction. It's something to do with your hands rather than scratch," Lio says. "I am okay with that, but it may have direct effect on the mechanisms of the itch itself."

Read more on Dr. Lio's CAMs at **bit.ly/managing-AD**

Alternative medicine for atopic dermatitis

Many patients with AD are turning to nontraditional treatments not backed by science.

PAT F BASS III, MD, MS, MPH

Atopic dermatitis (AD) is a common, chronic inflammatory disorder affecting 15% to 30% of pediatric patients.[1,2] In addition to itching, irritation, and redness of the skin, AD can have a tremendous impact on children, including in social and school situations. Research indicates stress levels in treating and caring for children with AD are greater than when caring for a child with diabetes.[3] The mainstay of current treatment is the use of topical steroids and calcineurin inhibitors. However, increasing numbers of patients and parents are turning to complementary and alternative treatments. Why is this so?

What is alternative medicine?

According to the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM), more than 40% of Americans use some form of complementary and alternative medicine—CAM.[4] Although often referred to as a single entity by many, CAM is actually 2 different concepts (Table 1). In complementary medicine, patients *combine* traditional, mainstream Western medicine with a nontraditional treatment approach. Nontraditional treatments are a diverse group of practices and can include dietary supplements, herbs, probiotics, homeopathy, traditional Chinese medicine, and mind/body practices such as meditation, acupuncture, and massage therapy. In alternative medicine, patients elect to use a nontraditional approach *in lieu of* treatment with traditional, mainstream Western medicine.

The complementary approach is much more common with patients using complementary treatments in an adjunctive fashion. However, patients often are very confused. Many patients do not realize that most CAM treatments are not evaluated by the US Food and Drug Administration (FDA) and are misled by statements that seem to be promising but often are void of scientific evidence. Although the NIH and NCCAM have begun funding studies examining CAM practices, it is important for pediatricians to realize that patients continue to consume CAM in large numbers despite a lack of clinical evidence.

Alternative medicine for atopic dermatitis

Use of CAM is increasing for a number of different medical conditions. Estimates for CAM use among asthmatic children average 60%.[5] A recent study analyzing data from the 2007 National Health Interview Survey found that nearly 47% of American children used a CAM treatment at some point.[6] In terms of AD, individual treatments each scored less than 1%, but these included a variety of therapies such as herbal therapy; vitamins; Ayurveda; naturopathy; homeopathy; traditional healing; diet and vegan-specific diet; and movement techniques (Table 2).

A number of smaller studies indicate a much higher CAM usage rate compared with what NIH and NCCAM report. Nearly 43% (34 of 80) of parents surveyed in 1 study said they gave their children herbal remedies and homeopathic products.[7]

Reasons parents report for using CAM with AD are varied. While one might think that all parents utilizing CAM are dissatisfied

TABLE 1 COMPLEMENTARY VS ALTERNATIVE MEDICINE

COMPLEMENTARY MEDICINE
- Combines traditional, mainstream Western medicine with nontraditional treatments

ALTERNATIVE MEDICINE
- Uses nontraditional treatments in lieu of traditional, mainstream Western medicine

NONTRADITIONAL TREATMENTS
- Dietary supplements
- Herbs
- Probiotics
- Homeopathy
- Traditional Chinese medicine
- Mind/body practices such as meditation, acupuncture, and massage

National Institutes of Health.[4]

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1. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. J Hum Nutr Diet. 2001;14(5):359-363

*Defined by Wessel's Rules of 3: crying that lasts 3 hours a day, for at least 3 days in a week, for 3 weeks

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TABLE 2 ALTERNATIVE TREATMENTS

- Herbal therapy
- Vitamins
- Ayurveda
- Naturopathy
- Homeopathy
- Traditional healing
- Diet and vegan specifically
- Movement techniques

Silverberg JI, et al.[6]

with traditional healthcare, many patients say they tried CAM on the recommendation of someone they trusted. Because there is currently no cure for AD and treatment primarily consists of symptomatic management, many patients with suboptimal control are dissatisfied and looking for a treatment that will work. Dissatisfaction may lead patients down the CAM path.[7]

Another common reason cited for patients trying CAM is the concern of potential adverse effects of traditional medical treatment for AD. Long-term use of topical steroids can lead to skin atrophy, depigmentation, and telangiectasia. Topical calcineurin inhibitors may lead to skin burning or irritation after topical use. Additionally, many doctors and parents are concerned over FDA warnings of potential cancer risks with calcineurin inhibitor use, and answers to this question are likely years away.[7]

These reasons drive home the importance of taking a good medication history, especially because many patients may not report CAM use like they do for other types of medication. Additionally, clinicians need to be comfortable educating parents about medication/CAM basics and appropriate use, and discussing any parental concerns.

Alternative therapy is not always helpful

Hon and colleagues report a recent case of an 11-year-old girl in which CAM was potentially harmful.[8] The girl had AD that was difficult to control and a previous history of treatment noncompliance. She had tried dietary avoidance and supplements, and was beginning to experience weight loss. Her family decided to bring her to an alternative medicine practitioner, and the patient and family embarked on a trial of cupping and acupuncture. This patient's treatment was complicated by blistering of the skin and a significant infection.

The literature is peppered with a number of bad outcomes that resulted in adverse effects after treating AD with alternative therapy.[7] Treatment with an unidentified herbal therapy for 8 months led to bilateral cataracts in an 11-year-old while a 2-week course of a Chinese herbal medicine led to a severe cardiomyopathy in another patient. Although adverse events are more commonly reported in adults, Lim and colleagues[9] examined the type of events impacting pediatricians' patients. They found that infants with restricted intake and children with chronic illness who had stopped their traditional treatments to pursue a CAM treatment were at highest risk for adverse effects. Pediatricians themselves also experienced a number of problems including: poor availability of product information when needed; ingredients of a product not being available; patients not knowing what products they were taking; and products containing multiple ingredients, making it difficult to determine what caused an adverse effect.

Although many patients assume that the term "natural" in the description of a CAM product means "safe," this is not necessarily so. These CAM products may interact with other CAM products or medications, thereby increasing or decreasing the amount of drug that may be available for treatment.

PATIENT EDUCATION

Resources on complementary and alternative medicines to review and share with your patients:

National Institutes of Health-National Center for Complementary and Alternative Medicine (NIH-NCCAM):
- **http://nccam.nih.gov/**

NCCAM's Time to Talk:
- **http://nccam.nih.gov/timetotalk**

Natural Medicines Comprehensive Database:
- **www.naturaldatabase.com**

Dr Bass is chief medical information officer and associate professor of medicine and pediatrics, Louisiana State University Health Science Center–Shreveport. The author has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

Find more CAM at **bit.ly/CAM-for-AD**

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Isotretinoin risks in acne treatment

Pediatricians should be forthright with patients and their families about the potential risks associated with use of isotretinoin for acne.

JOHN JESITUS

When it comes to isotretinoin, dermatology experts say, pediatricians should advise parents not to believe everything they read online. Furthermore, patients can't always be relied upon to comply with the birth-control requirements for using the drug.

IBD issues

Perhaps the most common misconception about isotretinoin, according to Bernard Cohen, MD, professor of pediatrics and dermatology at Johns Hopkins University School of Medicine, Baltimore, Maryland, is its possible association with inflammatory bowel disease (IBD). "Many people buy into that stuff," states Cohen, "especially people who look on the Internet."

Bernard Cohen, MD

Julie C. Harper, MD

Elaine Siegfried, MD

Julie C. Harper, MD, clinical associate professor of dermatology at the University of Alabama at Birmingham, offers an historical rationale for this misconception. "Early on, some large epidemiologic studies showed that perhaps there might be an association between isotretinoin and ulcerative colitis and IBD." However, she continues, those studies did not control for an underlying diagnosis of acne, or for the fact that most people treated with isotretinoin also have been treated with antibiotics. Such factors could act as confounding variables, Harper states.

She adds that later epidemiologic studies attempted to control for these variables. "And the most recent studies have not shown an association between IBD and isotretinoin."[1,2]

Cohen says that when he starts a child on isotretinoin, he alerts patients and parents to the potential connection. "But I also tell them that the best-done studies don't show a connection between use of isotretinoin for acne and IBD."

Elaine Siegfried, MD professor of pediatrics and dermatology at Saint Louis University, Missouri, adds that a well-done recent study actually showed isotretinoin to be protective against IBD.[3]

Contraceptive conundrum

With birth control pills typically prescribed under the US Food and Drug Administration (FDA)-mandated iPLEDGE risk management program, says Cohen, "People are worried about thromboembolic events, but they forget that pregnancy has a much higher risk than any of the birth control pills we use."

According to the package insert of 1 combined oral contraceptive (COC), a woman's risk of a venous thromboembolic event (VTE) doubles if she takes a COC—rising from approximately 3 per 10,000 women-years to 6 per 10,000 women-years. "If she takes an oral contraceptive pill (OCP) that contains drospirenone, it may triple—up to 9 per 10,000 women-years," Harper relates, "but if she gets pregnant, it rises to 12 per 10,000 women-years. If someone is sexually active and you give [her] a birth control pill, overall [she is] still choosing to lessen [her] risk of a blood clot. The risk is lower on the pill than if [she gets] pregnant."

Three OCPs—Estrostep (ethinyl estradiol [EE], norethindrone; Warner Chilcott; Rockaway, New Jersey); Ortho Tri-Cyclen (EE, norgestimate; Janssen Pharmaceuticals; Titusville, New Jersey); and YAZ (EE, drospirenone; Bayer Healthcare, Leverkusen, Germany)—are FDA approved for treating acne.

Cohen says that when he has a patient with moderately inflammatory acne who declines oral antibiotics or who flares without them, "One consideration might be to give her an OCP. Some people will argue that patients who flare during their menstrual periods will be more likely to respond to oral contraceptives" because their acne clearly has

a hormonal component.

Cohen believes that, in this setting, it's important to choose a contraceptive—and to counsel patients—carefully. For patients with a family history of thromboembolic events in young people, he avoids drospirenone whether or not the patient goes on isotretinoin. If the family history includes a parent or relative with severe acne who may have used isotretinoin, "The patient is at greater risk for developing more severe, persistent disease," Cohen emphasizes. "It's important to explain this at the first visit."

Siegfried typically puts postmenarchal females with acne on an OCP (unless contraindicated) after first screening for a family history of clotting and for other risk factors such as smoking. "I also ask the mother if she's ever been on hormonal therapy, and how she tolerated it," she states. If any concern arises, particularly a history of clotting, "I will refer the patient to my hematology colleagues for a thrombophilia evaluation" before prescribing hormonal therapy.

Assessing abstinence

If a 12-year-old girl needs isotretinoin, has had normal periods for a year, and says she is not sexually active, Harper reflects, "The question is, do you force her to go on an OCP, knowing [its] risks? Or do you allow this person to enter the iPLEDGE program" claiming to be sexually abstinent and reporting no other forms of contraception?

Siegfried states that she has taken the latter route for infants and young children. For women of childbearing age, however, her approach differs. "You do all you can to prevent pregnancy," she says, "but it is ultimately the patient's responsibility, after you have adequately informed [her]" about the necessity of always using 2 birth-control methods.

The data justify concern about patients' candor in this regard. In a survey that anonymously asked 75 patients how compliant they were with the birth-control choices they reported for iPLEDGE, Harper relates, "Many were not compliant.[4] For example, if they said they were going to use OCPs and a condom, they would only really use the OCP and not the condom, and they regularly missed pills. Additionally, in the group of women who said they were going to be abstinent, a fair number were not."

All study participants had reported being sexually active before entering the program, Harper notes. When a patient who previously has been sexually active says she is not currently in a relationship, Harper says, "Perhaps we should strongly encourage her to use a combination such as an OCP and condoms. Age may or may not play a role here. If a person says she's abstinent and has never been sexually active, that person may be a better choice" to rely on abstinence.

Cohen concludes that, for safety's sake, "I have to assume that all patients who are having periods are potentially sexually active."

Skeletal side effects

Regarding the concern of isotretinoin causing premature closure of epiphyseal plates, Harper says that evidence is scant to support the fears. "There's so much misinformation on the Internet," she says. "We have moms who come into the clinic with a child who has already been treated with every acne medication, and the child is not responding. In fact, the acne is getting worse, with evidence of scarring."

Yet when staff members begin enrolling the child in the iPLEDGE isotretinoin risk management program, she relates, "The parent says, 'Wait—I've heard that this drug will make children stop growing.'" Harper says that when one looks for data to support this claim, "You'll find that cases where there is premature closure of the epiphyseal plate occur in people who are on extremely high doses for many years for indications other than acne."

> ***"The best patient or parent is an informed one. So, all these issues—proven or unproven—should be discussed."*** ***—Bernard Cohen, MD***

Mr Jesitus is a medical writer based in Colorado. He has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

Read further at **bit.ly/isotretinoin**

FDA's sunscreen recommendations

The US Senate just approved a bill to speed up the FDA's approval of sunscreen ingredients. Here's guidance, cautions, and SPFs, decoded.

MARY BETH NIERENGARTEN, MA

The need to protect the skin from excessive sun exposure from ultraviolet radiation (UVR) is now well established based on studies showing a clear causal link between excessive UVR exposure and damage to the skin that raises the risk of skin cancer and leads to premature aging.[1] Despite this known causal link, the rate of skin cancer continues to grow at a rapid pace.

Data show that the incidence of the most serious type of skin cancer, melanoma, has been doubling every 10 years in many countries and is expected to continue to rise over the next 10 to 20 years.[1] In the United States, skin cancer is the most common cancer and it is estimated that 1 in 5 persons will be diagnosed with a skin cancer during his or her lifetime.[1]

Protecting children against sun overexposure is particularly important to prevent or reduce the lifetime chance of developing skin cancer and other skin damage. Epidemiologic data show a higher incidence of melanoma in persons with a history of sunburns during childhood, and data from a prospective, population-based study indicate that more than 50% of children experience a sunburn before age 11 years followed by another sunburn a few years later.[2]

Pediatricians can play a pivotal role in reducing the adverse effects of sun damage by educating children and their parents on ways to avoid overexposure to the sun, including the appropriate and regular use of sunscreen. When used along with other primary preventive measures, the appropriate use of sunscreen can provide the necessary protection to prevent and reduce the rising incidence of skin cancer.[2]

FAST FACT
1 in 5 persons will be diagnosed with a skin cancer in his or her lifetime.[1]

This article is a brief overview of current efforts to provide guidance on the proper use of sunscreen in children. The article first describes recent efforts by the US Food and Drug Administration (FDA) to provide guidance to consumers on how to evaluate the effectiveness of different sunscreen products based on mandating new regulations to sunscreen manufacturers on labeling requirements. Pediatricians and other healthcare providers can help their patients understand these labels to ensure the appropriate and best selection and use of these products.

Along with sunscreen use, the FDA and other organizations highlight the importance of using other primary preventive measures to provide the best protection against the sun as described. Finally, the article briefly mentions several issues that have raised some concerns regarding the potential harm of sunscreens, including systemic toxicity and vitamin D deficiency, as well as issues that await more clear FDA direction such as the safety of sunscreen sprays.

Recent FDA guidance on sunscreen use

With the growing number of sunscreens on the market with varying information on sun protection claims, the FDA proposed new regulations to sunscreen manufacturers to establish standards for testing the effectiveness of over-the-counter (OTC) sunscreen products.[3] Implemented in July 2012, the new regulations require that all sunscreen products be labeled to provide accurate information on the product's effectiveness.[4,5] Key terms and their descriptions used in labeling based on these new FDA regulations are listed in Table 1.[5,6]

Important to highlight is the label telling consumers that the product reduces the risk of all types of sun damage, including skin cancer. These products are labeled as broad spectrum with a sun protection factor (SPF) of 15 or greater, and the labeling further indicates that: "If used as directed with other sun protection measures, this product reduces the risk of skin cancer and early skin aging, as well as helps prevent sunburn."[5]

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References: 1. Holscher HD et al. *Bifidobacterium lactis* Bb12 enhances intestinal antibody response in formula-fed infants: a randomized, double-blind, controlled trial. *JPEN J Parenter Enteral Nutr*. 2012;36:106S-117S. **2.** Guinane CM et al. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. *Ther Adv Gastroenterol*. 2013;6:295-308. **3.** Alexander DD et al. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr*. 2010;50:422-430. **4.** US Food and Drug Administration. 100% whey-protein partially hydrolyzed infant formula and reduced risk of atopic dermatitis [letter]. http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm256731.htm. Issued May 24, 2011. Accessed August 1, 2014. **5.** von Berg A et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol*. 2013;131:1565-1573.

TABLE 1 TERMS IN SUNSCREEN LABELING BASED ON FDA REGULATIONS

TERM	FDA REGULATION	DESCRIPTION
SPF	○ Maximum claim for SPF allowed on a product: SPF 50+. ○ No evidence substantiates additional sun protection in products SPF >50. ○ Sunscreens with SPF >15 are more protective than those <15.	○ SPF provides numeric measurement of how effective sunscreen is in preventing sunburn, and typically ranges from 2 to >100. The assumption is that higher SPFs (ie, 30 vs 15) provide substantially better sun protection, but this may not be accurate.
Broad spectrum	○ Broad spectrum can only be used on a label if the product provides protection of both UVA radiation and UVB wavelengths, and protects against ≥90% of UV spectrum (290-400 nm). ○ Non-broad spectrum products or broad spectrum with SPF of 2–14 must be labeled: "These products have not been shown to protect against skin cancer and early skin aging. They have been shown only to help prevent sunburn." ○ Broad spectrum products with SPF ≥15 may be labeled: "If used as directed with other sun protection measures, this product reduces the risk of skin cancer and early skin aging, as well as helps prevent sunburn."	○ Protection against both UVA and UVB is important for sunscreen effectiveness. Historically, many sunscreen products only protected against UVB, which protects against sunburn. Protection against UVA and UVB is necessary to protect against skin cancer and premature skin aging.
Water resistance	○ Products needing to be reapplied after 40 min of swimming or sweating, or immediately after drying off, should be labeled water resistant. ○ Product needing to be reapplied after 80 min of swimming or sweating, or immediately after drying off, should be labeled very water resistant.	○ Products are differentiated as water resistant or very water resistant based on how well they retain stated SPF after undergoing immersion testing.
Waterproof or sweatproof	○ Cannot be used on labels.	
Immediate use or prolonged protection >2 hr	○ Neither label can be used unless data to support claim are submitted to and approved by the FDA.	

Abbreviations: FDA, US Food and Drug Administration; nm, nanometer; SPF, sun protection factor; UV, ultraviolet; UVA, ultraviolet A; UVB, ultraviolet B.
Food and Drug Administration[5]; US Food and Drug Administration.[6]

Preventive measures used with sunscreens

Along with selecting an appropriate sunscreen to prevent sun damage, children and their parents should be advised to follow several simple instructions that can minimize the risk of sun damage. Several organizations, including the FDA, emphasize the need for adhering to other preventive methods along with sunscreen use to provide the best sun protection. Most of these measures prioritize the need to reduce sun exposure particularly during midday when UV intensity is at its peak and emphasize the need to cover up with appropriate clothing while in the sun; regular use of ample sunscreen while in the sun; and application of a sunscreen sufficient to protect the skin. Table 2 lists recommendations for primary prevention of overexposure to the sun by the FDA, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics.[6-9]

Ms Nierengarten, a medical writer in St. Paul, Minnesota, has over 25 years of medical writing experience, coauthoring articles for *Lancet Oncology, Lancet Neurology, Lancet Infectious Diseases*, and Medscape. The author has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

More sunscreen guidance at **bit.ly/sunscreen-update**


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Talking about tattoos

Tattoo-associated skin complications are on the rise.

LISETTE HILTON

ConsumerReports.org reported in 2008 that tattoos had become mainstream. More than one-third of the US popoulation younger than 35 years have at least 1 tattoo, according to the article.[1]

The part of that statistic that most concerns pediatricians is that tattooing can result in complications, ranging from localized inflammatory skin eruptions to sometimes life-threatening infections and hepatitis. Some teenagers are at higher risk for complications than others.

Pediatricians who recognize and diagnose tattoo complications early on can help to prevent morbidity—even mortality. Pediatricians can also help by counseling their teenaged patients about potential dangers before children go under the needle.[2]

Physician awareness, surveillance, and action are needed, especially when one considers: "There is no standard regulation for training or licensing, no requirements for inspection, record-keeping, informed consent, or oversight for compliance and complications," according to *ConsumerReports.org*.[1]

A problematic process

It's no wonder that tattooing can result in skin and other health problems. Permanent tattooing involves making ink-filled injections into the dermis.[3]

The inks injected often consist of products that shouldn't be put into the body. Among those: azo pigments, which contain impurities and are manufactured for use as printing inks and automobile paint.[1] "Alarmingly, in tattooing, hundreds of milligrams are injected *directly* into the skin," according to *ConsumerReports.org*.

Even the water used in the tattoo ink or to dilute it is a potential health concern. Tattoo artists have been known to use distilled or reverse osmosis water to create or dilute tattoo ink products, which could expose adolescents and others to germs and infection.[4]

Cases in point

Researchers published a study in 2013 on increasing reports of cutaneous inoculation of nontuberculous (atypical) mycobacteria (NTM) during the tattooing process.[5] The 3 NTM skin infections reported in the study prompted the government to conduct an epidemiologic investigation.

Researchers in the study interviewed tattoo artists involved in the NTM cases about practices, ink procurement and use, and other symptomatic clients. They uncovered 31 cases of suspected or confirmed NTM inoculation from tattooing, and concluded the problem stemmed from a bottle of graywash ink used on the tattoos.[5]

Ms Hilton is a medical writer who has covered health and medicine for 25 years. She resides in Boca Raton, Florida. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

TATTOO TIPS FOR PATIENTS

To reduce infection, those seeking tattoos should:

- Use tattoo parlors approved/registered by their local jurisdictions.
- Request inks that are manufactured specifically for tattoos.
- Ensure that tattoo artists follow appropriate hygienic practices.
- Be aware of the potential for infection after tattooing and promptly seek medical care if skin problems occur.

For more information, visit the Centers for Disease Control and Prevention:
- **http://1.usa.gov/1ncZxtk**

Persons who experience a problem should notify the tattoo artist and the US Food and Drug Administration's MedWatch program:
- **www.fda.gov/Safety/MedWatch/default.htm**

For more safety tips, see the Nemours KidsHealth web page on tattoos:
- **http://kidshealth.org/teen/your_body/skin_stuff/safe_tattooing.html**

Read more on tattoos' health risks at **bit.ly/tattoo-risks**

LYMPHADENOPATHY LEADS TO HEART FAILURE

(116 beats per minute [bpm] and 113/58 mm Hg, respectively). Eyes and conjunctivae are normal appearing and moist; sclera are nonerythematous and anicteric. Tympanic membranes are bilaterally within normal limits. Mucous membranes are moist and pink. There are no lesions in the oropharynx. Cardiovascular examination indicates tachycardia with regular rhythm and no murmurs. Lungs are clear on auscultation. The abdomen is soft; the liver edge is palpable at the costal margin and the spleen is not palpated. Extremities move freely with no pain, swelling (tissue or joint), or edema. The skin is warm and well perfused with no rashes, desquamation, petechiae, or other lesions.

Examination of the neck is significant for an approximately 4 cm x 4 cm area of swelling below the right angle of the mandible. A smaller central area of induration is noted within the swelling and no fluctuance or erythema is observed. The mass is exquisitely tender and the patient has severely limited range of motion; he is unable to rotate or side bend right more than 10° and cannot flex his chin to his chest or extend greater than 25°. Despite this, neck stiffness is not present.

Initial laboratory findings

White blood cell (WBC) count is 42.5 x10^3/mm^3 (87% neutrophils on differential); C-reactive protein (CRP) concentration is 18.5 mg/dL; erythrocyte sedimentation rate (ESR) is 74 mm/hr; basic metabolic panel is within normal limits; and lactate dehydrogenase concentration is 226 U/L.

Differential diagnosis

There are several possible causes of unilateral neck swelling in children (Table 1). Based on the patient's history of upper respiratory tract infection and rapidly enlarging LN with a possible phlegmon developing on CT, you hypothesize that the patient has a straightforward case of postinfectious lymphadenitis.

You reason that lymphadenitis in your population is most commonly caused by Group A *Streptococcus* and *Staphylococcus aureus,* including methicillin-resistant *S aureus* (MRSA). However, the patient does have a history of contact with farm animals at a petting zoo, which opens up the possibility of animal-borne pathogens such as brucellosis. You decide to start IV clindamycin and observe.

An unexpectedly rocky hospital course

Over the 3 days following admission, the patient continues to have persistent fevers. Repeat labs are drawn and reveal that CRP has increased to 78 mg/dL; the WBC count has decreased marginally to 39 x 10^3/mm^3; and ESR has trended up to 100 mm/hr. By the third day of admission, the patient has developed persistent fevers, up to 102.4°F daily. The mass on the right side of his neck has modestly improved in size, although it does seem to coalesce with increased nodular induration centrally. At this point, the team reasons that either the antibiotic coverage is insufficient or the phlegmon has developed into an abscess that may require incision and drainage.

On the fourth day of admission, an infectious disease consult is obtained. Antibiotic regimen adjustment is recommended through the addition of a cephalosporin to clindamycin and augmenting with azithromycin to more broadly cover for MRSA, *Mycobacterium avium,* and *Bartonella henselae*. Further testing is performed that includes a broader panel of etiologic agents. A tuberculin purified protein derivative skin test is placed and serology is sent for *Bartonella*, *Brucella*, *Franscisella tularensis*, enteric cytopathic human orphan virus, *Enterovirus*, *Cytomegalovirus*, and *Parvovirus*, as well as for rheumatologic disorders. The team opts to change the antibiotic treatment to ampicillin with sulbactam and azithromycin.

Over hospital days 6 and 7, the patient continues to clinically deteriorate. He is noted to have decreased urine output (UOP), and has developed hypotension and worsening tachycardia. He has remained persistently febrile for the entire inpatient stay (7 days). Follow-up labs on day 7 reveal that the WBC count is slightly down (31 x10^3/mm^3) and CRP has increased to 177.5 mg/dL.

You receive a report on hospital day 7 when you return to service that the patient is now having persistently increasing tachycardia with hypotension unresponsive to fluid boluses. Administration of 1400 mL normal saline did not increase UOP, which has remained low at <1 cc/kg/hr. The patient is also complaining of joint pain, especially in his ankles and knees. As you round on the patient, you observe him walking from the bathroom back to bed and

TABLE 1 DIFFERENTIAL DIAGNOSIS FOR UNILATERAL NECK SWELLING

Infectious acute cervical lymphadenitis

Bacterial pathogens

- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Franscisella tularensis*
- Anaerobic bacteria

Infectious chronic/subacute cervical lymphadenitis

Bacterial pathogens

- Nontuberculous mycobacteria (scrofula)
- *Bartonella henselae* (cat-scratch disease)
- Brucellosis

Viral pathogens

- Epstein-Barr virus
- *Cytomegalovirus*

Connective tissue disease

Neoplasm

- Lymphoma
- Leukemia

Other syndromes

- Kawasaki disease
- Kikuchi disease
- PFAPA syndrome

Abbreviation: PFAPA, **p**eriodic **f**ever, **a**phthous **s**tomatitis, **p**haryngitis, **a**denitis.

he is notably short of breath. Vital sign measurements are significant for a heart rate of 152 bpm, blood pressure of 84/32 mm Hg, and normal temperature. You note that the patient has diminished breath sounds bilaterally in the lower lobes of the lungs, with mild crackles. You also note a new diastolic murmur and a possible gallop. Both hands and feet now appear to be swollen. Liver edge is palpable 2 cm below the costalphrenic margin. There are no rashes and mucous membranes remain moist. You are now concerned that your patient may be in acute heart failure.

A turning-point decision

Concerned about acute heart failure and possible shock, you order a stat electrocardiogram (EKG) and chest x-ray (CXR). While you wait for the results, you consider the various kinds of shock and where your patient might fit in:

Hypovolemic shock: History of volume loss, signs of poor peripheral perfusion, cool extremities, decreased distal pulses, small heart on CXR.

Septic shock/distributive shock: History of fever or immunocompromise; wide pulse pressure; variable peripheral perfusion: vasodilation in warm shock, vasoconstriction with cold shock; abnormal WBC count; disseminated intravascular coagulation.

Anaphylactic shock: History of exposure to an allergen (bee sting, food), stridor, wheezing, wide pulse pressure, vasodilation, urticaria, edema.

Neurogenic shock: History of trauma; hypotension with wide pulse pressure, normal heart rate, or bradycardia.

Cardiogenic shock: History of heart disease, central cyanosis, signs of heart failure (rales, hepatomegaly, gallop rhythm, jugular venous distention, heart murmur).

The EKG reveals sinus tachycardia and CXR is significant for increased perihilar infiltrates bilaterally. The radiologist does not comment on heart size, although it seems slightly large to you. The patient could feasibly be in either warm septic shock or cardiogenic shock; however, there is no apparent cause for either. Because the current antibiotic regimen does not cover MRSA, you are concerned about toxic shock syndrome or distributive, septic-like shock. Endocarditis is also a possibility, given the new murmur, albeit blood cultures have been negative thus far. You change antibiotics to clindamycin and ceftriaxone, as originally suggested by the infectious disease consult. Additionally, you schedule an echocardiogram and cardiology consult in the morning and add a brain natriuretic peptide (BNP) assessment to the morning labs.

By 3 AM, the patient is experiencing desaturations and has less than 0.5 cc/kg/hr UOP. You start IV furosemide and call cardiology to schedule priority evaluation. After initiation of furosemide, the patient has 1000 mL of urine output and is breathing much more comfortably. You now notice that the patient has bilateral erythematous conjunctivae. When you sign out to the morning attending you ask, "There's no way that we could be missing Kawasaki disease, is there?"

Diagnosis after a long night

The morning laboratory results return and cardiology performs a bedside echocardiogram, which reveals less than 34% systolic ejection fraction, with perivascular brightness of all coronary arteries, pericardial effusion, and mitral valve regurgitation.

Laboratory results are significant for CRP elevation to 217 mg/dL; an ESR of 101 mm/hr; BNP of 1507 pg/mL; and a WBC count of 36 x 10^3/mm^3.

Based on the echocardiogram results, the patient is diagnosed with incomplete Kawasaki disease (KD) with complication of acute heart failure from myocarditis. He is transferred to the pediatric intensive care unit (PICU) where he is placed on milrinone and dopamine and given intravenous immunoglobulin (IVIG). While in the PICU, he develops erythematous lips and continues to have bilateral hand and feet swelling. The family mentions to you that they had observed a brief macular rash during the patient's stay that they did not report to healthcare staff.

Discussion

Kawasaki disease is a classic pediatric condition bridging multiple classes of disease pathology and it is a critical clinical syndrome about which all pediatricians should have more than a cursory knowledge. It is recognized as both an unclassified infectious disease and a self-limiting vasculitis and is now the number one cause of acquired heart disease among children in the United States.[1]

In 1967, Dr. Tomisaku Kawasaki wrote his initial report on 50 cases of infants and children with a specific constellation of signs and symptoms, which some would say still comprises one of the most complete descriptions of KD and is the foundation for the clinical diagnostic criteria we use today.[2] The syndrome is characterized by fever; bilateral nonexudative conjunctivitis; erythema of lips and oral mucosa; changes in extremities; rash; and cervical lymphadenopathy. Despite 40 years and thousands of publications, the etiology of KD remains a mystery. Nonetheless, recognition and treatment are crucial because up to 25% of untreated children can develop coronary artery aneurysms that may lead to sudden death, myocardial infarction, or ischemic heart disease.[1]

Dr Darro is a pediatric resident, University of Nevada School of Medicine-Las Vegas Affiliated Hospitals. Dr Murray is a pediatric hospitalist, Sunrise Children's Hospital Pediatric Medical Group, Las Vegas, Nevada. Dr Patamasucon is professor of pediatrics, University of Nevada School of Medicine, Las Vegas. The authors have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

The diagnosis of this mystery patient continues online at **bit.ly/puzzler1014**

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(Requester Publications Only)
(Required by 39 USC 3685)

1. **Publication Title:** Contemporary Pediatrics
2. **Publication Number:** 8750-0507
3. **Filing Date:** 9/30/14
4. **Issue Frequency:** Monthly
5. **Number of Issues Published Annually:** 12
6. **Annual Subscription Price (if any):** $89.00
7. **Complete Mailing Address of Known Office of Publication:**
131 West First Street, Duluth, St. Louis County, Minnesota 55802-2065
Contact Person: Wendy Bong
Telephone: 218-740-7244
8. **Complete Mailing Address of Headquarters or General Business Office of Publisher:**
2501 Colorado Avenue, Suite 280, Santa Monica, CA 90404
9. **Full Names and Complete Mailing Addresses of**
Publisher: Samantha Armstrong 485F US Hwy 1S Suite 210 Iselin, NJ 08830
Content Channel Director: Teresa McNulty, Great Northern Corporate Center II, 24950 Country Club Blvd, North Olmsted, OH 44070
Content Managing Editor: Catherine Radwan, Great Northern Corporate Center II, 24950 Country Club Blvd, North Olmsted, OH 44070
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12. **Does Not Apply**
13. **Publication Title:** Contemporary Pediatrics
14. **Issue Date for Circulation Data Below:** August 2014
15. **Extent and Nature of Circulation**

	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
A. Total Number of Copies	**50,744**	**49,163**
B. Legitimate Paid and/or Requested Distribution		
1. Outside County Paid/Requested Mail Subscriptions Stated on PS Form 3541	**24,764**	**26,228**
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C. Total Paid and/or Requested Circulation (Sum of 15b (1), (2), (3), and (4))	**24,779**	**26,228**
D. Non-requested Distribution		
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2. In-County Non-requested Copies Stated on PS Form 3541	**0**	**0**
3. Non-requested Copies Distributed Through the USPS by Other Classes of Mail	**0**	**0**
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E. Total Non-requested Distribution (Sum of 15d (1), (2), (3) and (4))	**25,825**	**22,855**
F. Total Distribution (Sum of 15c and e)	**50,604**	**49,083**
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Name and Title of Editor, Publisher, Business Manager, or Owner:
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SECTION EDITOR

Pulse oximetry
The fifth vital sign

As pediatricians, we should appreciate the pulse oximetry technology we use every day to screen for hypoxemia and the efforts of the researchers responsible for its development

It is easy to take for granted some of the technologies we use every day. The pulse oximeter was invented 40 years ago and has become such a routine part of medical practice that oximetry measurements have often been referred to as the "fifth vital sign." This article takes a look at the brief history of pulse oximetry, describes how the technology works, and details the nuances of using pulse oximetry in everyday pediatric practice.

From humble beginnings

Modern day pulse oximetry had its beginnings in avionics research. In the early days of high altitude flight, it was important to study the effects of cabin pressure on the oxygenation of blood in the circulatory system of pilots. In 1935, Karl Matthes, a German scientist, introduced the first ear oxygen saturation meter using 2 photo sensors and lights initially in the red and green wavelengths, subsequently changed to light in the red and infrared wavelengths. Several years later, a US scientist, Glenn Millikan, produced a lightweight *portable* ear oxygen meter for use in pilots. It was Millikan who coined the term *oximeter* to describe his device.[1] The oximeter was first commercialized in the 1960s by Hewlett Packard (Palo Alto, California) who sold a $10,000 device for use in pulmonary and sleep laboratories.

It was not until the early 1970s that 2 Japanese bioengineers, Takuo Aoyagi and Michio Kishi, serendipitously discovered that the transmission of the red and infrared frequencies of light through an earlobe showed variations corresponding with the pulsatile flow of arterial blood perfusing the tissue. They established that by measuring the pulsatile component of light transmission through living tissues they could eliminate the variable absorption of light by bone, skin, and venous circulation. They also discovered that the transmission of light in the red and infrared wavelengths could be used to calculate oxygen saturation in the arterial circulation of tissue being analyzed.[2]

The first *pulse oximeter*s were manufactured in Japan in the late 1970s by Nihon Kohden and Minolta, but their clinical utility was unknown at the time. Following studies indicating that these devices could have widespread medical applications, pulse oximeters were commercialized in the United States in 1981 by Biox/Ohmeda (Ohmeda Medical; Boulder, Colorado) and by Nellcor (Covidien; Mansfield, Massachusetts) in 1983.[3]

The devices began to be used clinically, mostly by anesthesiologists to monitor patients undergoing sedation and anesthesia. Over the next several years, accumulated data indicated that pulse oximeters could prevent 2000 to 10,000 anesthesia deaths each year from undetected

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hypoxemia. In 1986, the American Society of Anesthesiologists recommended that these devices be used to monitor patients undergoing anesthesia.[4] Over the next decade, pulse oximetry spread from the operating room to the emergency department, and then came to be used routinely in medical offices.

Oximetry measurements

An oximetry sensor consists of red and infrared light-emitting diodes and a photodetector placed on opposite sides of a measurement site, usually the finger in adults and children but the palm or foot in neonates and toddlers. The ratio of red to infrared light that passes through the tissue depends on the percentage of oxygenated versus deoxygenated hemoglobin in the arterial circulation of the tissue. In turn, the percentage of oxygen saturation displayed by a pulse oximeter is determined by an algorithm in the microprocessor of the device based on saturation measurements obtained by sampling a large population of patients breathing mixtures of decreased oxygen concentrations.

These algorithms are unique for each manufacturer. Pulse oximeters take hundreds of readings over a 3- to 6-second time period and update their measurements every 0.5 to 1 second.[2] In the best of circumstances, pulse oximeter readings come within 2% to 3% of those produced by co-oximetry, the measurement of arterial blood directly by a blood gas analyzer.

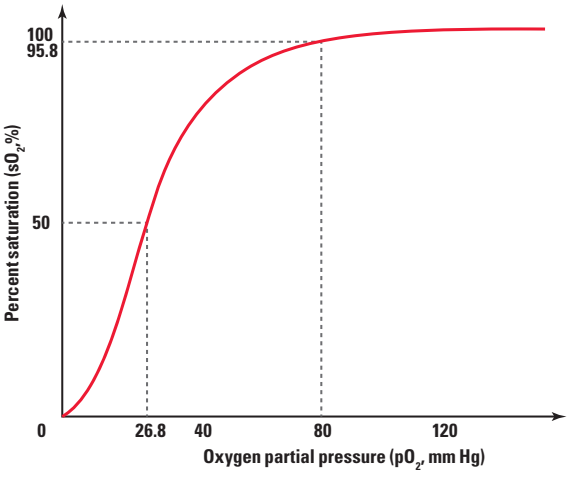
When using oxygen saturation clinically, it is important to recall the oxygen dissociation curve we learned in medical school (Figure). The upper "bend" in the oxygen dissociation curve occurs at a pO_2 of 60 mm Hg of oxygen, which corresponds to an oxygen saturation of 90%. Therefore, one needs to be aware that saturation levels of 90% and below are associated with hypoxemia.

In the office, we use pulse oximetry to determine whether a patient has respiratory compromise, that is, when evaluating a child presenting with symptoms of pneumonia, bronchiolitis, croup, and asthma. Pulse oximetry helps determine the severity of respiratory distress and is used to monitor how well patients respond to treatment. It should be our goal to achieve a pulse oximetry reading of 92% or higher in our patients, and to be aware of the many conditions that can interfere with oximeter readings.

For the extended version of this article with references, go to bit.ly/pulse-ox

FIGURE

OXYHEMOGLOBIN DISSOCIATION CURVE



Oxygen partial pressure (pO_2, mm Hg)	Oxygen saturation (SaO_2, %)
100	99
80	95.8
60	90
50	26.8

TABLE

LIMITATIONS OF PULSE OXIMETRY

CONDITION	CONSEQUENCE
Poor perfusion associated with dehydration, cold environment, shock	Oximeter may not be able to produce readings under low perfusion conditions.
Nail polish, artificial nails	Inaccurate readings or oximeter may not be able to produce readings.
Movement (seizure, tremors, shivering, wiggling)	Oximeter may not be able to produce readings with motion.
Anemia, carbon monoxide poisoning	Oxygen delivery to tissues is reduced, despite normal oximeter readings.
Bright lights	May be associated with falsely low oximeter readings.

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Advertising Index

CONTINUED FROM PAGE 50

dermcase } CALCIFIED HEEL NODULES

Heel nodules resulting in calcinosis cutis are caused by the pathological deposition of calcium phosphate in the skin.[1] Calcified heel nodules in infants have been linked to heel sticks since 1979.[2] These white or yellow papulonodular lesions typically appear at 4 to 12 months[3]; may be solitary or multiple[4]; and can range from 1.5 mm to 5 mm in diameter.[1,5-9] The surrounding skin appears normal without erythema or other signs of inflammation.[3,4]

Earlier reports have described these lesions as asymptomatic,[3] but more recently there have been accounts of children presenting with nodules that were tender upon contact with footwear.[4,8,9]

Lesions usually resolve without treatment by 18 to 30 months.[3] The nodules often migrate to the surface and extrude through the epidermis.[1,3] However, sometimes the lesions may either recur or persist and there are cases that describe children presenting with these nodules at 4, 5, and even 7 years of age.[4,9]

Epidemiology

The main risk factor for the development of these nodules is exposure to numerous heel sticks in the neonatal period.[3] Babies at highest risk are usually premature; have a low birth weight; experience respiratory distress or other complications; and spend time in the NICU. However, several investigators also have described calcified heel nodules in full-term infants with uncomplicated birth histories,[5,6,8] one of whom developed a lesion after only 1 heel stick[8] whereas others were pricked up to 8 times.[6]

There are not enough cases reported to reliably estimate the incidence or determine whether there is a gender or racial bias.

Etiology

There are 2 main theories that exist regarding the etiology of calcified heel nodules. Some researchers describe these lesions as dystrophic calcifications that occur secondary to trauma.[4] Tissue damage induced by the heel stick causes the release of alkaline phosphatase, which increases pH and creates conditions that favor the precipitation of calcium phosphate. An alternate theory suggests that the nodules are calcified epidermal implantation cysts.[7] Children with this condition have normal serum calcium and phosphate levels.[4,6]

Differential diagnosis

Calcified heel nodules may resemble milia, staphylococcal pustulosis, and herpes simplex virus (HSV) infection. To diagnose this condition, a history of heel sticks with the typical clinical findings in a healthy child is usually sufficient.[4] A radiograph may confirm calcification. Staphylococcal or HSV infection may be ruled out by Gram stain or Tzanck smear, respectively, as well as appropriate cultures, but these lesions would typically be painful and acute in onset. Whereas milia are common in newborns, they typically occur on the face and resolve within the first 2 to 4 months.

Treatment

Calcified heel nodules are usually self-limiting, so no treatment is needed[1] unless the lesions are tender and the child is in distress. There are no official guidelines on how to treat symptomatic nodules. Several methods have been described in case reports. In one case, removal by curettage with cauterization of the base led to a recurrence 5 months later, thus requiring subsequent deep curettage with local anesthetic to eliminate the lesion.[4] In another case, removal by punch biopsy was more successful, with no recurrence reported in the 4-year follow-up period.[7]

Our patient

Because our patient's lesions were asymptomatic, reassurance was provided to the parents. The child will return for follow-up as needed. Interestingly, she has a monozygotic twin who had a similar NICU course but has not developed heel stick nodules. Although calcified heel nodules have been reported in both monozygotic twins,[4] this is the first report of the lesions occurring in only 1 twin. ■

Ms Kryatova is a second-year medical student at Johns Hopkins University School of Medicine, Baltimore, Maryland. **Dr Cohen**, section editor for Dermcase, is professor of pediatrics and dermatology, Johns Hopkins University School of Medicine, Baltimore.
The author and section editor have nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article. Vignettes are based on real cases that have been modified to focus on key teaching points. Images also may be edited or substituted for teaching purposes.

For references, go to **bit.ly/dermcase1014**

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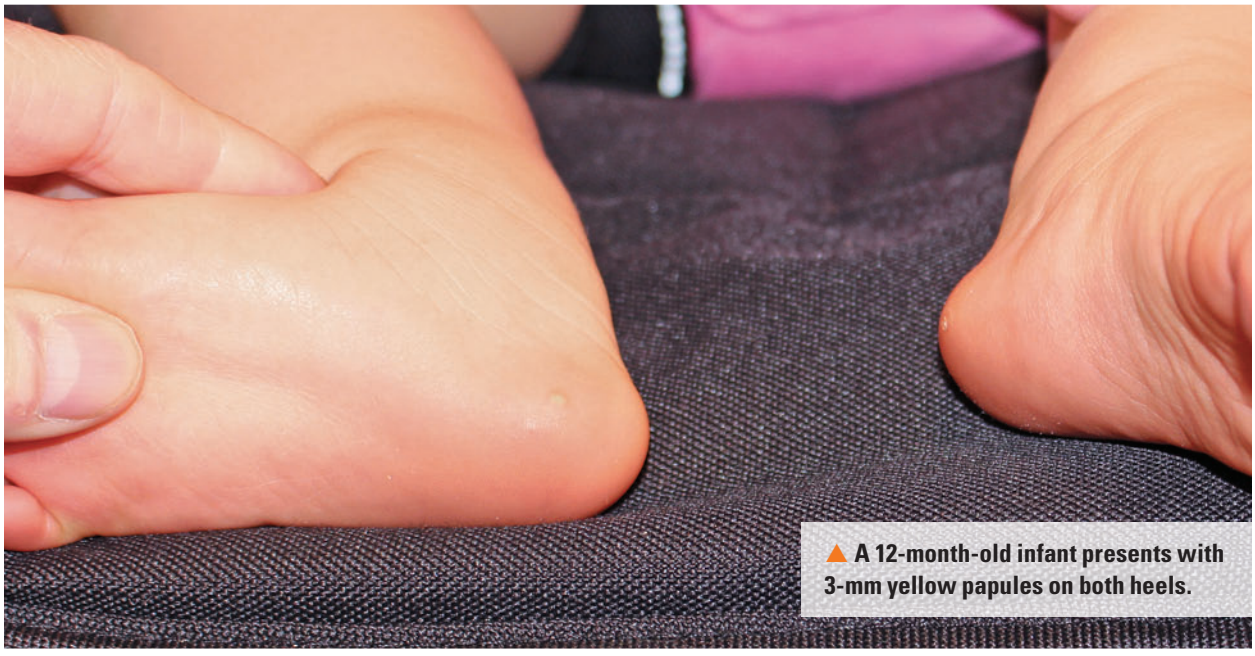

▲ A 12-month-old infant presents with 3-mm yellow papules on both heels.

Curious yellow bumps on a baby's heels

MARIA KRYATOVA, BS, MS2

THE CASE

The parents of a healthy 12-month-old girl are worried about yellow bumps that have been present on the baby's heels for 7 months. She was born at 34 weeks and spent 10 days in the neonatal intensive care unit (NICU). Since then she has grown and developed normally. FOR MORE ON THIS CASE, TURN TO PAGE 49. ▶

IMAGE CREDIT / AUTHOR SUPPLIED

DERMCASE *diagnosis* } CALCIFIED HEEL NODULES

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WARNINGS: EpiPen and EpiPen Jr Auto-Injectors should **only** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK. Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.

Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Treatment should be directed at vasodilation in addition to further treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection.

DO NOT INJECT INTRAVENOUSLY. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

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PRECAUTIONS:

(1) General

EpiPen and EpiPen Jr Auto-Injectors are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

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The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, pediatric patients under 30 kg (66 lbs.) body weight using EpiPen Auto-Injector, and pediatric patients under 15 kg (33 lbs.) body weight using EpiPen Jr Auto-Injector.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr Auto-Injector to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

(2) Drug Interactions

Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentoloamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.

(3) Carcinogenesis, Mutagenesis, Impairment of Fertility

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Studies of epinephrine after repeated exposure in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of epinephrine under the conditions noted under **INDICATIONS AND USAGE.**

(4) Usage in Pregnancy

Pregnancy Category C: There is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rabbits at a dose of 1.2 mg/kg daily for two to three days (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m^2 basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 4 days (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). Although, there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known if epinephrine passes into breast milk.

ADVERSE REACTIONS: Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs **[see PRECAUTIONS, Drug Interactions]**. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area **(see WARNINGS).** Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

Rx only.

MANUFACTURED FOR Mylan Specialty L.P., Basking Ridge, NJ 07920, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company.

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EPI-2014-0143

EpiPen 2-Pak® EpiPen Jr 2-Pak®
(Epinephrine) Auto-Injectors 0.3/0.15mg

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INDICATIONS

EpiPen® (epinephrine) 0.3 mg and EpiPen Jr® (epinephrine) 0.15 mg Auto-Injectors are indicated in the emergency treatment of type 1 allergic reactions, including anaphylaxis, to allergens, idiopathic and exercise-induced anaphylaxis, and in patients with a history or increased risk of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to body weight.

IMPORTANT SAFETY INFORMATION

EpiPen Auto-Injectors should only be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK, OR INTRAVENOUSLY.

Epinephrine should be used with caution in patients with certain heart diseases, and in patients who are on drugs that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders,

IMPORTANT SAFETY INFORMATION (CONTINUED)

diabetes, and hypertension, may be at greater risk for adverse reactions. Other adverse reactions include transient moderate anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

EpiPen and EpiPen Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy only and are not intended as a substitute for immediate medical or hospital care.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For additional information please contact us at 800-395-3376 or visit epipen.com/professionals.

PLEASE SEE BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION ON THE ADJACENT PAGE

1. Data on file, BusinessOne National Aggregates, as of 12/2013. Mylan Specialty LP, 2013.

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